

201-14222



To: Oppt.ncic@epamail.epa.gov  
cc: Jane Vergnes <JVergnes@ispcorp.com>, Christopher Bradlee <bradlec@basf-corp.com>

Subject: HPV Submission CASNO 107-19-7

Attached is the HPV submission for Propargyl alcohol CASNO 107-19-7. There are three attachments in pdf format:

1. Cover letter
2. Test plan
3. Robust summaries

This submission is made on behalf of the BPPD Consortium (regional)

Please call or email me if you have any difficulty receiving or opening the submission.

**Elmer Rauckman PhD DABT**

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**618-539-5280**



107-19-7-CL.pdf



107-19-7-TP.pdf



107-19-7-RS.pdf

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December 30, 2002

Christine Todd Whitman  
US Environmental Protection Agency  
PO Box 1473  
Merrifield VA 22116

Re: Submission of Propargyl Alcohol (CASNO 107-19-7) Documents

Via Electronic Submission to [Oppt.ncic@epa.gov](mailto:Oppt.ncic@epa.gov)

Registered with EPA as:

BPPB Consortium, **Registration Number**

Dear Administrator Whitman;

On behalf of the Propargyl Alcohol Consortium, I am submitting the attached test plan and robust summaries for Propargyl Alcohol (CASNO 107-19-7), submitted under the United States Environmental Protection Agency's High Production Volume Chemical Challenge Program. This submission consists of a test plan and a set of robust summaries for this material.

The Consortium members sponsoring this submission are

- ☐ BASF Corporation
- ☐ International Specialty Products

This document is being submitted in electronic format (Adobe Acrobat pdf files). If you require additional information or have problems with the electronic document please contact me as a representative of the Consortium by phone (618-539-5280) or email ([erauckman@charter.net](mailto:erauckman@charter.net)).

Sincerely,

Elmer Rauckman, PhD, DABT  
Consulting Toxicologist

Attachments:

Testing Plan      107-19-7-TP.pdf  
Robust Summaries   107-19-7-RS.pdf

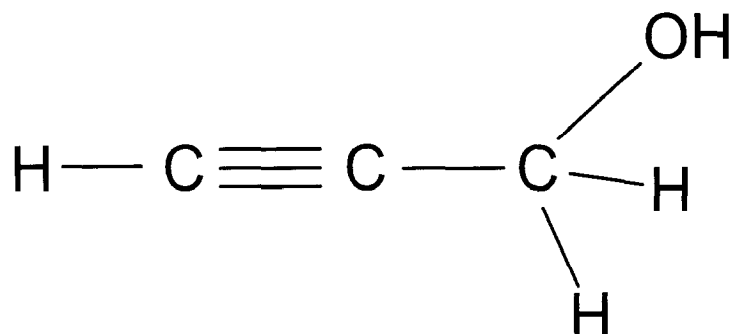
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## Propargyl Alcohol



CAS Number 107-19-7

## U.S. EPA HPV Challenge Program Submission

December 30, 2002

Submitted by:

**Propargyl Alcohol Consortium**

Prepared by:  
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## Table of Contents

Executive Overview .....	3
Testing Plan and Rationale .....	4
Introduction.....	6
Metabolism, Mechanism of Action and Pharmacokinetics .....	7
<i>Mechanism of Activation and Metabolism</i> .....	7
<i>Figure 1. Proposed Bioactivation and Metabolism of Propargyl Alcohol</i> .....	8
Physicochemical Data.....	9
<i>Table 1: Physicochemical Properties of Propargyl Alcohol</i> .....	9
Environmental Fate and Pathways.....	9
Ecotoxicity .....	10
<i>Table 2: Aquatic Toxicity of Propargyl alcohol</i> .....	11
Health Effects .....	11
Acute Toxicity .....	11
<i>Oral Exposure</i> .....	11
<i>Inhalation Exposure</i> .....	12
<i>Dermal Exposure</i> .....	12
Repeat Dose Toxicity .....	13
<i>Table 3: Repeated-dose Toxicity Studies of Propargyl Alcohol</i> .....	13
<i>Oral Exposure</i> .....	13
<i>Inhalation Exposure</i> .....	13
<i>Dermal Exposure</i> .....	14
Genetic Toxicity .....	14
<i>Genetic Toxicology in vitro</i> .....	14
<i>Genetic Toxicology in vivo</i> .....	15
Reproductive Toxicity .....	15
Developmental Toxicity .....	16
Conclusions.....	16
References.....	17

## Executive Overview

Propargyl alcohol CAS no. 616-45-4 is a three-carbon acetylenic alcohol, which can be prepared by several routes. It is a clear liquid with a geranium-like odor and with moderate volatility. It is miscible with water and polar organic solvents. The freezing point is in the range of -50° C, the boiling point at 1013 hPa is 114-115° C, the vapor pressure at 20°C is 15.5 hPa and its log  $K_{ow}$  is -0.35. Its uses span a wide range of applications including, reactant/chemical intermediate, corrosion inhibitor, solvent stabilizer, soil fumigant and polymer modifier.

In the environment, based on physicochemical data and experimental data, Propargyl alcohol will not bioaccumulate and will distribute primarily to water where it will be subject to volatilization and biodegradation. It is expected to react rapidly with atmospheric hydroxyl radicals with a half-life of 12 hours. As there are no consumer applications for Propargyl alcohol, and as the material degrades in a wastewater treatment plant, there should be no significant releases to water. The toxicity of Propargyl alcohol to aquatic species is moderate to high, with an  $LC_{50}$  for freshwater fish in the range of 1-5 mg/L.

Pharmacokinetic data show that Propargyl alcohol is rapidly absorbed and distributed after oral or inhalation exposure. Excretion is also rapid with extensive metabolism to carbon dioxide. The enzyme CYP 2E1 has been identified as primarily responsible for activation of Propargyl alcohol to its biologically reactive aldehyde.

Multiple determinations of the oral  $LD_{50}$  of Propargyl alcohol have been reported in a range of 50 to 100 mg/kg-bw. The approximate 1-hr  $LC_{50}$  for Propargyl alcohol has been established with relatively high confidence by a combination of two studies and is in the range of 1000-1200 ppm. The dermal  $LD_{50}$  has been reported as 88 mg/kg-bw in rabbits but dermal absorption can be low due to the volatility of this material.

There are several studies of Propargyl alcohol extending for 14 or 90-day periods by the three major routes of exposure. The systemic NOAEL is low with liver and kidney being target organs.

Genotoxicity studies have shown little potential for genotoxicity activity in vitro or in vivo. An inhalation carcinogenicity study in rats and mice is ongoing with the National Toxicology Program (start date 09/2001).

Although subchronic studies have not shown any specific damage to reproductive organs, there is no specific data available on the developmental or reproductive toxicity of Propargyl alcohol.

The overall conclusion is the information is adequate for all the HPV data elements except reproduction and development. An OECD 421 test is recommended to establish reliable information for these endpoints.

## **Testing Plan and Rationale**

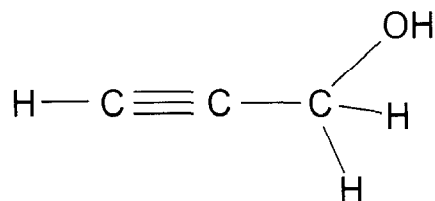
## Testing Plan in Tabular Format

CAS Number 107-19-7 Propargyl Alcohol		Information Available?	OECD Study?	GLP Study?	Supporting Information?	Estimation Method?	Acceptable?	Testing Recommended?
HPV Endpoint								
<b>Physical Chemical</b>								
Melting Point	Y	N	N	N	N	Y	N	
Boiling Point	Y	N	N	N	N	Y	N	
Vapor Pressure	Y	N	N	Y	N	Y	N	
Partition Coefficient	Y	Y	N	Y	N	Y	N	
Water Solubility	Y	N	N	Y	N	Y	N	
<b>Environmental &amp; Fate</b>								
Photo-Degradation	Y	N	N	N	Y	Y	N	
Water Stability	Y	N	N	Y	Y	Y	N	
Transport	Y	N	N	N	Y	Y	N	
Biodegradation	Y	N	N	Y	N	Y	N	
<b>Ecotoxicity</b>								
96-Hour Fish	Y	N	N	Y	N	Y	N	
24-Hour Invertebrate	Y	N	N	Y	N	Y	N	
8-Day Algae	Y	Y	N	Y	N	Y	N	
<b>Toxicity</b>								
Acute	Y	N	N	Y	N	Y	N	
Repeated Dose	Y	N	Y	Y	N	Y	N	
Genetic Toxicology <i>in vitro</i>	Y	N	N	Y	N	Y	N	
Genetic Toxicology <i>in vivo</i>	Y	Y	Y	Y	N	Y	N	
Reproductive	Y	N	Y	Y	N	N	Y	
Developmental	N	N	N	Y	N	N	Y	

## Introduction

Propargyl alcohol CAS no. 107-19-7 is a three-carbon acetylenic alcohol, which can be prepared by several routes. These include preparation from acetylene using a high-pressure synthesis (1) and as a by-product of the commercial synthesis of butynediol (2).

It is a clear liquid with a geranium-like odor. It has moderate volatility and is miscible with water and polar organic solvents. Its uses span a wide range of applications including, reactant/chemical intermediate, corrosion inhibitor, solvent stabilizer, soil fumigant and polymer modifier (12). Its structure is shown below:



Propargyl alcohol is also known as:

- ☐ Propynyl alcohol
- ☐ 2-Propynol
- ☐ 2-Propynyl alcohol
- ☐ 1-Hydroxy-2-propyne
- ☐ 1-Propyn-3-ol
- ☐ 1-Propyn-3-yl alcohol
- ☐ 3-Hydroxy-1-propyne
- ☐ 3-Propynol
- ☐ Ethynylcarbinol

Exposure in industrial applications is limited by process controls and protective equipment. Inhalation and dermal exposure are considered the primary routes of occupational exposure. The ACGIH TLV is 1 ppm with a skin notation. The basis for this TLV is stated as the similarity of Propargyl alcohol to Allyl alcohol in structure and in

toxicity (3). There are no known consumer uses for Propargyl alcohol; thus, no consumer exposure is known to occur.

Several physicochemical, fate and toxicity studies have been conducted on Propargyl alcohol. These studies are briefly reviewed in this testing rationale document, which also describes how these studies meet the SIDS (Screening Information Data Set) end-points of the United States Environmental Protection Agency (USEPA) High Production Volume Challenge (HPV) program. Robust summaries have been prepared for key studies; supporting studies are referenced in these summaries or given as shorter summaries using the IUCLID format. The available data set satisfactorily fulfills most of the data requirements for the EPA HPV Program.

The majority of data elements are filled by high-reliability studies on Propargyl alcohol, where direct data are not available or data are sparse, surrogates and estimation are used to fill the data element where appropriate. This is encouraged by the U.S. EPA and other regulatory authorities to avoid unnecessary testing cost and animal usage. After review of the existing data and examination of surrogates and modeling, the data elements for reproductive and developmental toxicity remain unfilled.

## **Metabolism, Mechanism of Action and Pharmacokinetics**

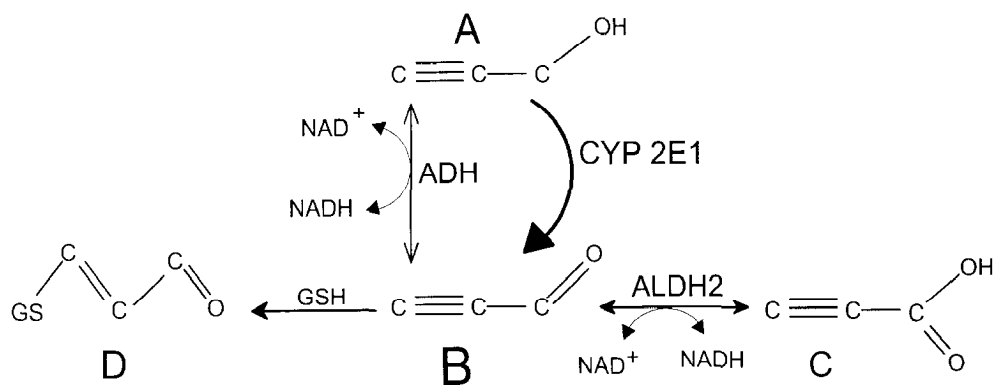
Absorption-Distribution-Metabolism-Excretion (ADME) data developed by the National Toxicology Program (4) show that Propargyl alcohol is quickly distributed and excreted following an intravenous dose. The majority of the radioactivity ( $^{14}\text{C}$ -labeled test material) was excreted in the urine and as carbon dioxide in the breath of both rats and mice. Oral dosing resulted in a similar rapid (but slower than after i.v. dosing) excretion pattern, with the bulk of radioactivity being excreted in the urine and exhaled carbon dioxide. Dermal absorption was low due to the volatility of Propargyl alcohol. Inhalation exposure resulted in 55 to 63% absorption of inhaled Propargyl alcohol at 1 or 10 ppm and only 23-33% absorption at 100 ppm. Both species eliminated the majority of the inhaled dose in urine. Chromatographic analysis indicated that Propargyl alcohol is extensively metabolized and one metabolite was identified as a glutathione conjugate. It was assumed that there are multiple glutathione conjugates across the triple bond as was demonstrated by Banijamali et al. in a recent publication (5)

## **Mechanism of Activation and Metabolism**

Studies in the mid 1990's by DeMaster and coworkers (6) reported that, while oxidative metabolism of low molecular weight primary alcohols is generally accepted to be catalyzed by alcohol dehydrogenase, Propargyl alcohol is a relatively poor substrate for this enzyme. They studied the metabolism of Propargyl alcohol by the catalase alternative pathway. Bovine liver catalase was used, to measure the rate of oxidative bioactivation of Propargyl alcohol to 2-Propyn-1-ol. They found the rate to be higher than predicted by modeling and

hypothesized that the oxidative biotransformation of Propargyl alcohol to the more reactive  $\alpha,\beta$ -unsaturated aldehyde by liver catalase might be the initial step in Propargyl alcohol induced liver injury.

Moridani and coworkers (7) recently showed that inactivation of catalase in isolated hepatocytes only partially inhibited the toxicity of Propargyl alcohol. They went on to demonstrate that Propargyl alcohol-induced cytotoxicity, rapid GSH depletion and reactive oxygen species (ROS) formation involves metabolic activation by cytochrome P450 rather than catalase or alcohol dehydrogenase. Using specific induction and depletion they demonstrated that CYP 2E1 was the enzyme responsible for activation of Propargyl alcohol to its aldehyde, 2-Propyn-1-al. This is in contrast to the activation of Allyl alcohol, which is oxidized to its cytotoxic aldehyde, Acrolein, by alcohol dehydrogenase. They postulated the metabolic scheme below based on their data:



**Figure 1. Proposed Bioactivation and Metabolism of Propargyl Alcohol**

In this scheme, Propargyl alcohol (A) is oxidized primarily by CYP 2E1, with a minor contribution by alcohol dehydrogenase, to 2-Propyn-1-al (B). The aldehyde is a chemically active species that can attack vital cellular macromolecules but reacts preferentially with glutathione to form conjugates that undergo urinary excretion. An alternative pathway for the aldehyde is further enzymatic oxidation via aldehyde dehydrogenase to Propiolic acid (C), which could be further, oxidized, conjugated and excreted, or be converted back into the aldehyde. Its ability to react with glutathione and cellular macromolecules is not known.

Mechanistically, they demonstrated depletion of glutathione and formation of ROS (Reactive Oxygen Species), which lends support to the proposed mechanism. This mechanism is also consistent with the recent NTP ADME results present briefly above, is coherent with basic chemical and biochemical principles and is consistent with the organ effects (liver as primary systemic target) seen in the subchronic studies. A relatively-high degree of dermal toxicity is also predicted by this model as oral administration would be expected to result in significant "first-pass

metabolism” whereas dermal administration should lead to relatively higher concentrations in the CNS that could effect mortality in experimental animals.

This mechanism is considered highly plausible and is supported by the known data. Some details, such as the role of the Propolic acid (which could be biochemically active, as it has potential for 1,4-addition type reaction) and distribution of the aldehyde remain to be elucidated.

## Physicochemical Data

Physicochemical data for Propargyl alcohol are available from the literature and are confirmed by manufacturer’s information.

Melting Point	-52 to -48° C (8)
Boiling Point	114 - 115° C @ 1013 hPa (8)
Vapor Pressure	15.5 hPa @ 20° C (9)
Partition Coefficient	Log $K_{o/w}$ = -0.35 (10)
Water Solubility	Soluble in all proportions (8)

**Table 1: Physicochemical Properties of Propargyl Alcohol**

These properties indicate that Propargyl alcohol is a moderately volatile liquid with high water solubility. The value of the partition coefficient suggests that Propargyl alcohol will partition preferentially into water and, therefore, has little potential for bioaccumulation.

**Recommendation:** No additional physicochemical studies are recommended. The available data fill the HPV required data elements.

## Environmental Fate and Pathways

Biodegradation potential for Propargyl alcohol has been determined using a BOD20 test which provided a 20-day BOD:COD ratio of 0.61 (11). The kinetics were measured at 5 and 10 days where the BOD/COD ratio was 0 and 0.39, respectively. The source or adaptation state of the inoculum was not disclosed but this result indicates that Propargyl alcohol can be rapidly biodegraded by a wastewater treatment plant.

This result is supported by the BIOWIN (v4.00) estimate that predicts rapid biodegradation from all of its models (see robust summary). Overall the data are sufficient to demonstrate that this material is biodegradable, but it is

not known if it can be considered “readily biodegradable” by the OECD criteria. As there are no consumer uses for this chemical intermediate the relevant consideration is biodegradation in a wastewater treatment plant and this has been demonstrated.

Photodegradation was estimated using version 1.90 of the Atmospheric Oxidation Program for Microsoft Windows (AOPWIN) that estimates the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. The estimated rate constant is used to calculate atmospheric half-lives for organic compounds based upon average atmospheric concentrations of hydroxyl radical. The program produced a estimated rate constant of  $10.4 \text{ E-12 cm}^3/\text{molecule-sec}$ . Using the default atmospheric hydroxyl radical concentration in APOWIN and the estimated rate constant for reaction of Propargyl alcohol with hydroxyl radical, the estimated half-life of Propargyl alcohol vapor in air is approximately 12.3 hours (see accompanying robust summary). Based on the structure, it is also estimated that Propargyl alcohol vapor will react with atmospheric ozone but this reaction will be insignificant compared with the hydroxyl radical reaction rate.

Water stability has not been quantitatively determined for Propargyl alcohol. Quantitative stability determinations (e.g. OECD 111) are considered unnecessary for compounds containing only non-hydrolysable groups, as the SIDS manual states that consideration should be given to using an estimation method. There is no evidence available that Propargyl alcohol is unstable in water, and it has no hydrolysable groups. Both the alkyene and alcohol moieties are considered generally resistant to hydrolysis by Harris (12). A more thorough rationale is presented in the attached robust summary.

Theoretical Distribution (Fugacity) of Propargyl alcohol in the environment was estimated using the MacKay EQC level III model with standard defaults in EPIWIN v 3.05 but using the measured vapor pressure and the measured  $\log K_{ow}$  (13). The results for distribution using a model calculated  $K_{oc}$  (adsorption coefficient based on organic carbon content) of 0.183 and equal initial distribution to air, water and soil are:

○ Air	3.1 %
○ Water	53.6 %
○ Soil	43.2 %
○ Sediment	0.09 %

**Recommendation:** No additional fate studies are recommended. The available data fill the HPV required endpoints.

## Ecotoxicity

Flow though studies of acute fish toxicity using measured concentrations of Propargyl alcohol are available demonstrating a moderate to high hazard ( $LC_{50} = 1.5 \text{ mg/L}$ ) to fathead minnows after 96 hours of exposure. A static test using the golden orfe provided a higher ( $4.6 \text{ mg/L}$ )  $LC_{50}$ . Daphnia studies indicate an  $EC_{50}$  in the area

of 25 mg/L. The two values reported in the table below were obtained by the same investigators, using the same method except that reconstituted freshwater was used to generate the higher value and tap water to generate the lower value. Algae growth inhibition was determined using a standardized procedure as a threshold of toxicity value ( $EC_{03}$ ) to be 18 mg/L in an 8-day test. These values with references are shown in the table along with results of ECOSAR modeling using a specific model for the Propargyl alcohols that was developed by the U.S.EPA. Two sets of estimates are given; the first uses physiochemical parameters as calculated by the SRC software and the second as calculated by the CLOPG software (14). In this case, a measured  $K_{ow}$  value was used to run the ECOSAR prediction and there is no clear way to determine which SAR equation is more appropriate. Use of the neutral organics model gives much higher values due to there being a specific mechanism other than narcosis for aquatic toxicity (15)

<b>Table 2: Aquatic Toxicity of Propargyl alcohol</b>		
	Reported Values	ECOSAR Predictions
Fish, 96-hour $LC_{50}$	1.5 mg/L (16)	4.7 mg/L*
	4.6 mg/L (17)	8.5 mg/L**
Daphnia, 24-hour $EC_{50}$	32 mg/L (18)	11.4 mg/L*
	11 mg/L (19)	17.7 mg/L**
Algae, 8-day $EC_{03}$	18 mg/L (20)	17.7 mg/L*
Algae, 96-hour $EC_{50}$		117 mg/L**

\* Estimated using ECOSAR using Propargyl alcohols model based on SRC estimates (21)

\*\*Estimated using ECOSAR using Propargyl alcohols model based on CLOPG estimates (21)

Support that simple AB unsaturated alcohols have a relatively high degree of aquatic toxicity also comes from data on the analog Allyl alcohol which has been reported to have a 96-hour  $LC_{50}$  for fathead minnows of 0.32 mg/L and a 96-hour  $EC_{50}$  for *Daphnia magna* in the range of 0.25 to 0.4 mg/L (22).

**Recommendation:** No additional ecotoxicity studies are recommended. The available data fill the HPV required endpoints.

## Health Effects

### Acute Toxicity

#### Oral Exposure

Multiple determinations of the oral  $LD_{50}$  of Propargyl alcohol have been reported. Perhaps the most reliable was published in 1985 by Archer (23), who reported an  $LD_{50}$  of 110 mg/kg-bw for male Sprague-Dawley rats and an  $LD_{50}$  of 55 mg/kg-bw for females of the same strain. These results are confirmed by additional studies one

reporting an LD<sub>50</sub> of 93 mg/kg for male and 54 mg/kg for female Sprague-Dawley rats (24) and the other reporting an LD<sub>50</sub> of 56 mg/kg for rats of unspecified sex and strain (25). All of these studies may be found as robust summaries accompanying this test plan.

### **Inhalation Exposure**

The approximate 1-hr LC<sub>50</sub> for Propargyl alcohol has been established with relatively high confidence by a combination of two studies. The first study, published in 1977 by Vernot (24), contains acute toxicity data for several compounds by different routes of administration. As they conducted analytical measurements on exposure levels and ran enough exposure levels to collect sufficient data for a high-confidence determination, confidence in the results is increased. Their results indicate that female rats are slightly more sensitive than males with a 1-hour LC<sub>50</sub> of 1040 ppm for females and 1200 ppm for males. The second study was a modern 1-hour limit test conducted at Hazleton Laboratories. In this study using measured concentrations of Propargyl alcohol, it was found that exposure of rats to 1480 ppm for one hour resulted in 100% mortality within a few days of exposure (26). This finding of an LD<sub>100</sub> at 1480 is in accord with the LC<sub>50</sub> being in the ranges of 1040-1200 ppm.

Although a standardized 4-hour LC<sub>50</sub> is not available, this material is anticipated to follow a C times T relationship reasonably well as the mechanism of death is not simply solvent narcosis. In this case, the 4-hour LC<sub>50</sub> can be estimated to be between 200 and 400 ppm with high confidence.

### **Dermal Exposure**

The dermal LD<sub>50</sub> of Propargyl alcohol was reported to be 88 mg/kg-bw in rabbits by Vernot in his many-route, multi-compound publication (24). This is a reasonable value in light of the oral and inhalation toxicity data. An interesting note to the potential dermal toxicity is a report that the LD<sub>10</sub> for Propargyl alcohol was 15.8 mg/kg- bw when the substance was applied in a solution of Dowanol-50 (27). These glycol ether types of solvents (Dowanol-50 is Dipropylene glycol monomethyl ether) are thought to enhance the penetration of materials through the skin, or at least interfere with the normal evaporation of the test substance. Based on the strength of these data the skin warning is appropriate for the bulk liquid material.

**Recommendation:** No additional acute studies are recommended. Although the available studies do not meet the requirements of the current OECD guidelines in most cases the available data fill the HPV required endpoints for acute toxicity. Conduct of additional acute toxicity studies would not add significantly to our understanding of this material's toxicity.

## Repeat Dose Toxicity

There are several studies of Propargyl alcohol extending for 14 or 90-day periods by the three major routes of exposure. For the purposed of hazard and risk assessment the 90-day studies were reviewed relative to the HPV requirements. The table below summarizes the most important study by each route.

Route	Species	Sex	Organs Affected	Local NOAEL	Systemic NOAEL	Ref
Gavage	Rat	M	Liver, kidney		5 mg/kg	IRIS (28)
		F	Liver, kidney		5 mg/kg	
Inhal	Rat	M	Liver, kidney	16 ppm*	16 ppm	NTP (29)
		F	Liver, kidney	16 ppm*	16 ppm	
	Mouse	M	Liver, kidney	8 ppm	4 ppm	
		F	Liver, kidney	32 ppm	16 ppm	
Dermal	Rat	M	None		13.3 mg/kg	GAF (30)
		F	None		13.3 mg/kg	

\* Excluding hyperplasia of the nose

**Table 3: Repeated-dose Toxicity Studies of Propargyl Alcohol**

### Oral Exposure

The U.S.EPA sponsored an oral-gavage study in Sprague-Dawley rats of each sex using dose levels of 0, 5, 15 or 50 mg/kg (28). Administration of 15 or 50 mg/kg-day of Propargyl alcohol to rats for 13-weeks was associated with significant adverse effects on the liver and kidneys at 50 mg/kg and potentially adverse effects seen by histopathology at 15 mg/kg-day. The 50 mg/kg-day dose in males was also associated with reduced body weight gain, 20% mortality and reduction in hemoglobin, mean corpuscular volume and corpuscular hemoglobin. The low-dose, 5 mg/kg-day, was a NOAEL for rats of each sex. It should be noted that males appeared to be the more sensitive sex under these conditions as opposed to females, which were more sensitive in the acute studies.

### Inhalation Exposure

The National Toxicology Program has completed 14-day and 13-week inhalation studies of Propargyl alcohol in Fischer 344 rats and B6C3F1 mice of each sex (29). In the rat studies, the most sensitive endpoint was hyperplasia associated with the respiratory epithelium of the nose. Necrosis and atrophy of the respiratory epithelium was also observed along with weight changes in the liver and kidneys. Excluding the nasal hyperplasia and a decrease in cholinesterase, the NOAEL was 16 ppm for males and females.

In the mouse studies the livers and kidneys were also affected along with the respiratory epithelium. In addition, the two high-dose level (32 and 64 ppm) groups of mice had reduced red blood cells and hemoglobin. The NOAEL for male mice was 4 ppm and the NOAEL for female mice was 16 ppm.

### **Dermal Exposure**

A study using dermal exposure of rabbits was conducted using a dosing regime of four administrations per day. That is the daily dose was divided into four equal portions and painted on the skin at four daily intervals. The dose levels (daily) were 1, 3 or 13.3 mg/kg and, other than minor skin irritation at the site of application, no adverse effects were observed that were associated with treatment (30).

**Recommendation:** No additional repeated-dose studies are recommended. The available data, much of which is modern and was conducted under GLP, fill the HPV required endpoint for repeated-dose toxicity.

### **Genetic Toxicity**

The SIDS/HPV requirement for genetic toxicity screening is for two end-points: generally one sensitive to point mutation and one sensitive to chromosomal aberrations. In the case of this material, adequate tests have been conducted that cover both of these endpoints.

#### **Genetic Toxicology in vitro**

Two *Salmonella typhimurium* reverse mutation assays, run with the standard strains and typical protocol, show lack of mutagenic activity in the presence or absence of metabolic activation (31). There is, however, a report in the literature that in an unusual strain of *S. typhimurium* (strain D3052), in the absence of metabolic activation, Propargyl alcohol was a weak mutagen (15 revertants/mmol). As this is a strain with an intact excision repair, but without plasmid pKM101 that codes for the errorprone repair enzyme of the SOS system. The observed weak mutagenicity did not increase in the presence of a metabolic activation (32). The results do not fit in with the standard strains used in the typical assays. There is also a notation in the NTP Chemical Status Report for Propargyl alcohol that it is positive in Salmonella (33). The NTP Salmonella data show that strain TA100 gave a weak positive response in the absence of metabolic activation when water was used as the solvent but not when DMSO was used as the solvent for the test substance. Also there was no positive response in the presence of metabolic activation using either induced rat or hamster liver S9. The overall call for mutagenicity of Propargyl alcohol was “negative” (34). At the request of the NTP, the data are not presented in a robust summary and only the results are included.

In a chromosome aberration test using CHO cells, cells collected 16 h following treatment with Propargyl alcohol showed a small but statistically significant increase in chromosomal aberrations in the absence of metabolic activation. Although only the response at the highest dose was significantly higher than the control, there was a

positive trend. In the presence of metabolic activation, a larger, dose-related increase was induced. This effect was confirmed in two repeat experiments. In cells sampled 10 h following treatment, there was no increase in chromosomal aberrations, either with or without metabolic activation (35).

### **Genetic Toxicology in vivo**

Mammalian genotoxicity was assessed *in vivo* using the mouse micronucleus test by at least two investigators. In an OECD-Guideline-474 study, a single gavage dose of Propargyl alcohol did not result in an increase in polychromatic erythrocytes containing micronuclei. It was concluded that the test material did not show genotoxic activity in this system (36). Another study in mice using two daily gavage doses of 0, 24, 48 or 72 mg/kg also gave negative results (35). In addition the NTP Chemical Status Report for Propargyl Alcohol also lists this material as negative in the micronucleus test (33). The NTP micronucleus data are from groups of 10 male and female mice exposed to either 0 or 64 ppm Propargyl alcohol for polychromatic erythrocytes; or exposed to 0, 4, 8, 16, 32 or 64 ppm Propargyl alcohol for normochromatic erythrocytes, by inhalation for 90 days. There was no increase in the number or percent of micronucleated cells (37)

**Summary and Evaluation:** Although there are some weak positive results in the “in vitro” testing, the *in vivo* data from three micronucleus studies done under different dosing regimes indicate that these *in vitro* effects are not important *in vivo*.

**Recommendation:** The SIDS requirement for genetic testing has been met as assays sensitive to both point mutation and to clastogenic effects have been conducted using acceptable protocols. No additional testing is recommended.

### **Reproductive Toxicity**

Examination of the reproductive organs after subchronic exposure to systemically toxic levels of Propargyl alcohol did not reveal any specific adverse effects on the reproductive organs of male or female animals. Data relative to the early events in developmental toxicology were not found.

**Recommendation:** It is recommended that additional data be generated that would be informative of the early events of development.

## Developmental Toxicity

Some of the available data are potentially informative concerning the possibility of developmental toxicity by Propargyl alcohol. Specific developmental toxicity relies on the ability of Propargyl alcohol (or a metabolite of Propargyl alcohol) to gain access to the conceptus and then either a special sensitivity of developing tissue or the ability of the conceptus to bioactivate the molecule. Relative contributions of detoxifying systems in the conceptus are also a consideration. None of the available information precludes Propargyl alcohol from having the potential to gain access to the conceptus and to be bioactivated. The pharmacokinetics data indicate wide distribution of material (4), although the conceptus has not been specifically evaluated, it cannot be excluded. The putative activating enzyme CYP2E1 is expressed in the human fetus by 18 weeks of gestation (38). It has been proposed that fetal CYP2E1 has a different spectrum of activity and perhaps a different amino-acid sequence than adult enzyme, and this is actively under investigation (38). Sulik and coworkers are investigating the role of CYP2E1 in early embryos relative to the activation of ethanol (39). They are using knockout mice and have described planned research evaluating the role of free radical species and free radical protective systems in the conceptus.

The current mechanistic work will be informative but these results are unlikely to provide information that would definitively indicate that Propargyl alcohol is not a potential developmental toxin.

**Recommendation:** It is recommended that a developmental toxicity screening study be performed to obtain reliable information concerning the potential of Propargyl alcohol to induce specific developmental toxicity.

## Conclusions

With regard to the parameters specified in the EPA HPV Challenge program, the available information fills all of the requirements for physicochemical parameters, fate, aquatic toxicity, acute and repeated-dose toxicity and genotoxicity. Other than data indicating lack of specific effects of Propargyl alcohol on reproductive organs, no reliable information on reproductive and developmental toxicity was found. For this reason, it is recommended that an OECD 421 "Reproductive/Developmental Toxicity Screening Test" be conducted on Propargyl alcohol. Based on the ADME results showing effective absorption and distribution by both oral and inhalation routes, either route could be effectively utilized.

---

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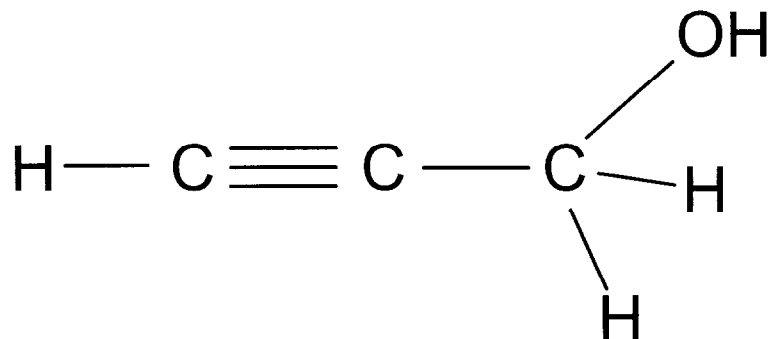
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-

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201-142228

## Propargyl Alcohol



**CAS Number 107-19-7**

Existing Chemical	: ID: 107-19-7
Memo	: Propargyl alcohol
CAS No.	: 107-19-7
Common name	: Propargyl alcohol
EINECS Name	: prop-2-yn-1-ol
Molecular Weight	: 56.06
ELINCS number	: 203-471-2
Molecular Formula	: C3 H4 O
Status	:
Memo	:
Printing date	: 31.12.2002
Revision date	:
Date of last update	: 31.12.2002
Number of pages	: 40
Chapter (profile)	: Chapter: 1.0.1, 1.2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6.1, 3.1.1, 3.1.2, 3.3.1, 3.3.2, 3.5, 4.1, 4.2, 4.3, 4.4, 5.1.1, 5.1.2, 5.1.3, 5.1.4, 5.4, 5.5, 5.6, 5.7, 5.8.1, 5.8.2
Reliability (profile)	: Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	: Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

## 1. General Information

Id 107-19-7

Date 31.12.2002

### 1.0.1 APPLICANT AND COMPANY INFORMATION

Type : lead organisation  
Name : Toxicology and Regulatory Affairs  
Contact person : Elmer Rauckman  
Date :  
Street : 1201 Anise Court  
Town : 62243 Freeburg, Illinois  
Country : United States  
Phone : 618-539-5280  
Telefax :  
Telex :  
Cedex :  
Email : rauckman@toxicsolutions.com  
Homepage : toxicsolutions.com

Remark : This document has been prepared on behalf of the Propargyl Alcohol  
Producers Consortium

Participating Members

BASF Corporation  
International Specialty Products

31.12.2002

### 1.2 SYNONYMS AND TRADENAMES

## 2. Physico-Chemical Data

Id 107-19-7

Date 31.12.2002

### 2.1 MELTING POINT

Value : = -52 - -48 °C

Test substance :

Propargyl alcohol, CASNO 107-19-7

Reliability :

(2) valid with restrictions

Handbook data are assigned reliability of 2

09.12.2002

(23)

### 2.2 BOILING POINT

Value : = 114 - 115 °C at 1013 hPa

Test substance :

Propargyl alcohol, CASNO 107-19-7

Reliability :

(2) valid with restrictions

Handbook data are assigned reliability of 2

09.12.2002

(23)

### 2.3 DENSITY

Type : relative density

Value : = .9715 at 20 °C

Test substance :

Propargyl alcohol, CASNO 107-19-7

Reliability :

(2) valid with restrictions

Handbook data are assigned reliability of 2

09.12.2002

(23)

### 2.4 VAPOUR PRESSURE

Value : = 15.5 hPa at 20 °C

Test substance :

Propargyl alcohol, CASNO 107-19-7

Reliability :

(2) valid with restrictions

Handbook data are assigned reliability of 2

09.12.2002

(25)

Value : = 20.75 hPa at 25 °C

Remark :

Given in reference as 15.6 mm Hg, converted to hPa

Test substance :

Propargyl alcohol, CASNO 107-19-7

Reliability :

(2) valid with restrictions

Handbook data are assigned reliability of 2

09.12.2002

(13)

## 2. Physico-Chemical Data

Id 107-19-7

Date 31.12.2002

### 2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water  
Log pow : = -.35 at 25 °C  
pH value :  
Method : OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"

Year :  
GLP : no data  
Test substance :

Test substance :  
Propargyl alcohol, CASNO 107-19-7

Reliability : (1) valid without restriction  
Modern guideline study

30.12.2002 (6)

Partition coefficient : octanol-water  
Log pow : = -.38 at 25 °C  
pH value :

Test substance :  
Propargyl alcohol, CASNO 107-19-7

Reliability : (2) valid with restrictions  
15.12.2002 (17)

### 2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water  
Value : at °C  
pH value :  
concentration : at °C  
Temperature effects :  
Examine different pol. :  
pKa : at 25 °C  
Description :  
Stable :

Result :  
Miscible with water, benzene, chloroform, ethanol, 1,2-dichloroethane, ether, acetone, dioxane, tetrahydrofuran, pyridine; moderately sol in carbon tetrachloride

Test substance :  
Propargyl alcohol, CASNO 107-19-7

Reliability : (2) valid with restrictions  
Handbook data are assigned reliability of 2

09.12.2002 (23)

Solubility in : Water  
Value : > 1000 g/l at 20 °C  
pH value : = 7  
concentration : 330 g/l at 20 °C  
Temperature effects :  
Examine different pol. :  
pKa : at 25 °C

## 2. Physico-Chemical Data

Id 107-19-7

Date 31.12.2002

<b>Description</b>	:	
<b>Stable</b>	:	
<b>Result</b>	:	Miscible
<b>Test substance</b>	:	Propargyl alcohol, CASNO 107-19-7
<b>Reliability</b>	:	(4) not assignable
		Study not available for review
09.12.2002		(7)
<b>Solubility in</b>	:	Organic Solvents
<b>Value</b>	:	at °C
<b>pH value</b>	:	
<b>concentration</b>	:	at °C
<b>Temperature effects</b>	:	
<b>Examine different pol.</b>	:	
<b>pKa</b>	:	at 25 °C
<b>Description</b>	:	
<b>Stable</b>	:	
<b>Result</b>	:	Miscible with water, benzene, chloroform, ethanol, 1,2-dichloroethane, ether, acetone, dioxane, tetrahydrofuran, pyridine; moderately sol in carbon tetrachloride
<b>Test substance</b>	:	Propargyl alcohol, CASNO 107-19-7
<b>Reliability</b>	:	(2) valid with restrictions
		Handbook data are assigned reliability of 2
09.12.2002		(23)

### 3. Environmental Fate and Pathways

Id 107-19-7

Date 31.12.2002

#### 3.1.1 PHOTODEGRADATION

Type : air  
Light source :  
Light spectrum : nm  
Relative intensity : based on intensity of sunlight

##### INDIRECT PHOTOLYSIS

Sensitizer : OH  
Conc. of sensitizer : 1500000  
Rate constant : = .000000000001 cm<sup>3</sup>/(molecule\*sec)  
Degradation : = 50 % after 12.3 hour(s)  
Deg. product :  
Method :  
Year :  
GLP : no  
Test substance :

Method : AOP v1.90 (EPIWIN) calculation  
Remark :

Based on the structure, it is also estimated that Propargyl alcohol vapor will react with atmospheric ozone but this reaction will be insignificant compared with the hydroxyl radical reaction rate. The estimated half life for reaction with ozone is 382 days using the EPA default ozone concentration and the APOWIN predicted reaction rate constant.

Result :  
AOP Program (v1.90) Results:

=====

SMILES : C#CCO  
CHEM : Propargyl Alcohol  
MOL FOR: C3 H4 O1  
MOL WT : 56.06

##### ----- SUMMARY (AOP v1.90): HYDROXYL RADICALS -----

Hydrogen Abstraction = 3.2690 E-12 cm<sup>3</sup>/molecule-sec  
Reaction with N, S and -OH = 0.1400 E-12 cm<sup>3</sup>/molecule-sec  
Addition to Triple Bonds = 7.0000 E-12 cm<sup>3</sup>/molecule-sec  
Addition to Olefinic Bonds = 0.0000 E-12 cm<sup>3</sup>/molecule-sec  
Addition to Aromatic Rings = 0.0000 E-12 cm<sup>3</sup>/molecule-sec  
Addition to Fused Rings = 0.0000 E-12 cm<sup>3</sup>/molecule-sec

OVERALL OH Rate Constant = 10.4090 E-12 cm<sup>3</sup>/molecule-sec  
HALF-LIFE = 1.028 Days (12-hr day; 1.5E6 OH/cm<sup>3</sup>)  
HALF-LIFE = 12.331 Hrs

##### -- SUMMARY (AOP v1.90): OZONE REACTION -----

OVERALL OZONE Rate Constant = 0.003000 E-17 cm<sup>3</sup>/molecule-sec  
HALF-LIFE = 382.000 Days (at 7E11 mol/cm<sup>3</sup>)

Experimental Database: NO Structure Matches

Source : Toxicology and Regulatory Affairs Calculation, 2002  
Test substance :

Reliability : Propargyl alcohol, CASNO 107-19-7  
(1) valid without restriction  
Calculated by an acceptable method.

Flag : Critical study for SIDS endpoint  
31.12.2002

(14)

### 3. Environmental Fate and Pathways

Id 107-19-7

Date 31.12.2002

#### 3.1.2 STABILITY IN WATER

Type : abiotic  
t1/2 pH4 : at °C  
t1/2 pH7 : at °C  
t1/2 pH9 : at °C  
Degradation : < 50 % after 1 year at pH and °C  
Deg. product :  
Method : other: Estimation based on chemical principles  
Year : 2002  
GLP : no  
Test substance :

Method :  
The stability of this material in water is estimated based on established chemical principles.

Result :  
Both the alkyne and alcohol moieties are considered generally resistant to hydrolysis by Harris (J.C. Harris in Lyman W, Reehl, W and Rosenblat, D. Handbook of Chemical Property Estimation Methods. American Chemical Society, Washington D.C. 1990, page 7-6). This indicates a hydrolytic half-life of greater than one year.

There is no chemical interaction between the alcohol and the alkyne that would facilitate the reaction of this substance with water. Reaction with water occurs either by a unimolecular process (Sn1 mechanism) or a bimolecular process (Sn2 mechanism).

In the unimolecular process, the initial reaction is dissociation of the chemical into an anion and a cation that is capable of undergoing nucleophilic attack by water. In the case of Propargyl alcohol, the only dissociation reactions available only form anions on either the terminal carbon center or the oxygen center. Either is unlikely as the pKa for the alcohol is in the range of 14-18 and the pKa for the terminal alkyne is in the range of 25 (see Vollhardt, K. "Organic Chemistry" WH Freeman and Co, New York, 1987). Furthermore the parent compound form an anion and not a cation that can be attacked by water.

In the bimolecular process it is necessary for there to be an electrophilic center capable of undergoing attack by a nucleophile. The only electrophilic center is the carbon attached to the hydroxyl group. Attack there by hydroxyl anion leads only to hydroxyl exchange and no change chemical structure.

In summary, Propargyl alcohol is considered resistant to hydrolysis and will have an environmental hydrolytic half-life of greater than one year.

Test substance : Propargyl alcohol, CASNO 107-19-7 purity 97% (source: Aldrich Chemicals)

Reliability : (2) valid with restrictions  
Estimate based on acceptable chemical principles

Flag : Critical study for SIDS endpoint

14.12.2002

(15)

### 3. Environmental Fate and Pathways

Id 107-19-7

Date 31.12.2002

#### 3.3.2 DISTRIBUTION

**Media** : air - biota - sediment(s) - soil - water  
**Method** : Calculation according Mackay, Level III  
**Year** : 2002

**Method** : Determined using the Level 3 EQC Model found in EPIWIN 3.05. Actual values were used for measured physicochemical parameters. The degradation times applied using the BIOWIN were considered reasonable based on limited data and surrogate compounds.

**Result** : Level III Fugacity Model (Full-Output):  
=====

Chem Name : Propargyl Alcohol  
Molecular Wt: 56.06  
Henry's LC : 1.15e-006 atm-m3/mole (Henry database)  
Vapor Press : 11.7 mm Hg (user-entered)  
Log Kow : -0.35 (user-entered)  
Soil Koc : 0.183 (calc by model)

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	3.11	24.6	1000
Water	53.6	360	1000
Soil	43.2	360	1000
Sediment	0.0896	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	1.13e-010	733	260	24.4	8.68
Water	4.59e-011	862	448	28.7	14.9
Soil	1.35e-009	696	0	23.2	0
Sediment	3.82e-011	0.36	0.015	0.012	0.000499

Persistence Time: 279 hr  
Reaction Time: 365 hr  
Advection Time: 1.18e+003 hr  
Percent Reacted: 76.4  
Percent Advected: 23.6

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):

Air: 24.61  
Water: 360  
Soil: 360  
Sediment: 1440  
Biowin estimate: 3.235 (weeks)

Advection Times (hr):

Air: 100  
Water: 1000  
Sediment: 5e+004

**Source** : Toxicology and Regulatory Affairs Calculation 2002  
**Test substance** :

Propargyl alcohol, CASNO 107-19-7  
**Reliability** : (1) valid without restriction  
Calculated by an acceptable method using measured physicochemical parameters.

**Flag** : Critical study for SIDS endpoint  
30.12.2002

(14)

### 3. Environmental Fate and Pathways

Id 107-19-7

Date 31.12.2002

#### 3.5 BIODEGRADATION

Type : aerobic  
Inoculum :  
Contact time : 20 day(s)  
Degradation : = 61 (±) % after 20 day(s)  
Result :  
Kinetic of testsubst. : 5 day(s) = 0 %  
10 day(s) = 39 %  
20 day(s) = 61 %  
%  
%

Method : The available report only describes the results of a BOD test.  
Remark :

This result is supported by the BIOWIN v4.00 modeling results that predict rapid biodegradation.

Output summary:

BIOWIN (v4.00) Program Results:

=====

SMILES : C#CCO

CHEM : Propargyl Alcohol

MOL FOR: C3 H4 O1

MOL WT : 56.06

----- BIOWIN v4.00 Results -----

Linear Model Prediction : Biodegrades Fast

Non-Linear Model Prediction: Biodegrades Fast

Ultimate Biodegradation Timeframe: Weeks

Primary Biodegradation Timeframe: Days

MITI Linear Model Prediction : Biodegrades Fast

MITI Non-Linear Model Prediction: Biodegrades Fast

Calculated by Toxicology and Regulatory Affairs 2002. Summary output only shown.

Result :  
BOD 5 = 0  
BOD10 = 0.73  
BOD20 = 1.15

COD = 1.87  
THOD = 2.0

In this case the BOD20 is 61% of the COD indicating that effective biodegradation is taking place. This conclusion is also supported by the kinetics.

Test substance :  
Propargyl alcohol, CASNO 107-19-7

Reliability : (2) valid with restrictions  
Flag : Critical study for SIDS endpoint

31.12.2002

(26)

## 4. Ecotoxicity

Id 107-19-7

Date 31.12.2002

### 4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type : flow through  
Species : Pimephales promelas (Fish, fresh water)  
Exposure period : 96 hour(s)  
Unit : mg/l  
LC50 : = 1.53 measured/nominal  
Limit test : no  
Analytical monitoring : yes  
Method : other: ASTM  
Year : 1980  
GLP : no data  
Test substance :

Method : Exposure was accomplished using a continuous-flow dilutor. Twenty fathead minnows, 29 to 33 days old, were placed in each 2 liter tank. The flow rate was 25 ml/min using Lake Superior water which had been filtered and warmed. Fish were not fed during the exposure period.

Analysis of concentration was conducted by gas chromatography at 0, 24, 48, 72 and 96 hours.

Remark : This determination was part of a mechanistic study of several acetylenic alcohols conducted at EPA's Duluth Laboratory.

Result : The 96-hour LC50 for Pimephales promelas (fathead minnow) was determined to be 1.53 mg/l with a confidence limit of 1.49-1.56 mg/l

Loss of equilibrium was also reported as an effect.

Test condition : Flow-through bioassay with measured concentrations, 25.7 deg C, dissolved oxygen 6.8 mg/l, hardness 43.4 mg/l as calcium carbonate, alkalinity 40.8 mg/l calcium carbonate, and pH 7.72

Test substance : Propargyl alcohol, CASNO 107-19-7, purity >95%

Reliability : (1) valid without restriction  
Acceptable Publication, part of major study of similar compounds.

30.12.2002 (16) (28)

Type : flow through  
Species : Pimephales promelas (Fish, fresh water)  
Exposure period : 96 hour(s)  
Unit : mg/l  
LC50 : = 1.44 measured/nominal  
Limit test : no  
Analytical monitoring : yes  
Method : other: ASTM  
Year :  
GLP : no data  
Test substance :

Method : Flow-through bioassay with measured concentrations, 24.7 deg C, dissolved oxygen 6.9 mg/l, hardness 42.8 mg/l calcium carbonate, alkalinity 40.6 mg/l calcium carbonate, and pH 7.7.

## 4. Ecotoxicity

**Id** 107-19-7

**Date** 31.12.2002

**Result** : The 96-hour LC50 for Pimephales promelas (fathead minnow) was determined to be 1.44 mg/l with a confidence limit of 1.25-1.67 mg/l

Loss of equilibrium was also reported as an effect.

**Test substance** : Propargyl alcohol, CASNO 107-19-7, purity >95%

**Reliability** : (2) valid with restrictions  
Acceptable Publication

30.12.2002 (16)

**Type** : static

**Species** : Leuciscus idus (Fish, fresh water)

**Exposure period** : 96 hour(s)

**Unit** : mg/l

**LC0** : = 3.16

**LC50** : = 4.6

**LC100** : = 6.81

**Limit test** : no

**Analytical monitoring** : no

**Method** : other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische, DIN 38412, Teil 15

**Year** :

**GLP** : no

**Test substance** :

**Method** : Followed DIN guideline: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische, DIN 38412, Teil 15

**Result** : The number of fish dead at each observation is shown in the table:

	TIME (hours)			
Conc	24	48	72	96
0.00	0	0	0	0
1.00	0	0	0	0
1.47	0	0	0	0
2.15	0	0	0	0
3.16	0	0	0	0
4.64	0	0	0	4
6.81	0	0	10	10
10.0	0	5	10	10

The pH was determined at each observation and only varied from 7.4 to 7.7

Oxygen levels were in a range of 7.0 to 8.6 at all observations and concentrations.

**Test condition** : Dilution water was prepared by reconstituting demineralized tapwater with 344 mg/L CaSO<sub>4</sub>-2 H<sub>2</sub>O, 124 mg/L MgSO<sub>4</sub>-7 H<sub>2</sub>O, 70 mg/L Sodium bicarbonate and 3 mg/L potassium chloride. Total hardness was 2.6 mmol/L, alkalinity 2.2 mmol/L, oxygen > mg/L and pH 8+-0.1. The test-temperature was 20 +- 1deg C.

Containers were glass aquaria 30x22x24 cm containing 10L water for 10 fish. Details of the dosing-solution preparation were not given in the report. It is assumed that it was diluted in water since it is water miscible.

## 4. Ecotoxicity

Id 107-19-7

Date 31.12.2002

Ten fish (mean body weight 2.8 grams) per concentration were exposed to the following concentrations of test material. 0.00, 1.00, 1.47, 2.15, 3.16, 4.64, 6.81, 10.0 mg/L for 96 hours. Fish were examined at 24, 48, 72 and 96 hours.

Calculation of the LC50 was conducted by probit analysis after Finney (Probit Analysis, Cambridge University Press 3ed 1971)

**Test substance** : Propargyl alcohol, CASNO 107-19-7

**Reliability** : (1) valid without restriction  
Guideline study with good documentation

30.12.2002 (5)

**Type** : static

**Species** : Leuciscus idus melanotus (Fish, fresh water)

**Exposure period** : 48 hour(s)

**Unit** : mg/l

**LC0** : = .5

**LC50** : = 1.9

**LC100** : = 4.8

**Limit test** : no

**Analytical monitoring** : no data

**Method** : other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische, DIN 38412, Teil 15, Vorabdruck 1976

**Year** :

**GLP** :

**Test substance** :

**Method** : Followed DIN guideline: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische, DIN 38412, Teil 15

**Test substance** : Propargyl alcohol, CASNO 107-19-7

**Reliability** : (2) valid with restrictions  
Secondary source limits reliability to 2

30.12.2002 (21)

### 4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

**Type** : static

**Species** : Daphnia magna (Crustacea)

**Exposure period** : 24 hour(s)

**Unit** : mg/l

**EC0** : = 24

**EC50** : = 32

**EC100** : = 42

**Limit Test** : no

**Analytical monitoring** : no

**Method** : The dilution water was reconstituted freshwater prepared by dissolving individual salts in deionized water as stocks and diluting these into deionized water. The final concentration of salts in the dilution water was:

CaCl2-2 H2O	294 mg/L
MgSO4-7 H2O	123 mg/L
NaHCO3	65 mg/L
KCl	5.75 mg/L

## 4. Ecotoxicity

Id 107-19-7

Date 31.12.2002

The pH was 8 +/- 0.2 and the water was bubbled with air to saturate it with oxygen prior to starting the exposure.

Test containers were 50 ml beakers containing 20 ml water. Oxygen and pH levels were determined at the beginning and end of the 24-hour incubation time. The beakers were not sealed but were covered with filter paper and placed in an incubator at 20 deg C for the 24 hour exposure period.

Twenty daphnids (ten per container) were tested per group. The concentrations tested are not specified for the test materials in this publication (there are a large number) but it is noted that the dilution factor was initially 1:2 but if the result did not yield an EC0 and an EC100 that could be used to graphically determine the EC50, closer dilution factors were used. No analytical data on the actual concentrations are provided. EC50 values were determined graphically from the actual EC0 and EC100.

**Remark** : The data indicate a rather steep dose response relation for the test material. This increases the accuracy for the EC50 determination. The lack of analytical data for this somewhat volatile compound is a confounder; however, it is less important as the exposure time was only 24 hours.

**Result** : The EC50 graphically determined for propargyl alcohol was 32 mg/L with an EC0 of 24 mg/L and an EC100 of 42 mg/L.

**Test substance** : Propargyl alcohol, CASNO 107-19-7

**Reliability** : (2) valid with restrictions  
Published article with good detail by reliable investigators.

**Flag** : Critical study for SIDS endpoint

30.12.2002

(9)

**Type** : static  
**Species** : Daphnia magna (Crustacea)  
**Exposure period** : 24 hour(s)  
**Unit** : mg/l  
**EC0** : = 6.3  
**EC50** : = 11  
**EC100** : = 25  
**Limit Test** : no  
**Analytical monitoring** : no  
**Method** :  
**Year** :  
**GLP** : no  
**Test substance** :

**Method** : The dilution water was chlorine-free tap water with a hardness of 16 deg H, a pH of 7.6 to 7.8 that was saturated with oxygen by bubbling with air.

Test containers were 50 ml beakers containing 20 ml water. Oxygen levels were determined at the beginning and end of the 24-hour incubation time. The beakers were covered with filter paper and placed in an incubator at 20-22 deg C for the 24-hour exposure period. Lighting was ambient from the laboratory.

Thirty daphnids, less than 24 hours old, (ten per container) were tested per

## 4. Ecotoxicity

Id 107-19-7

Date 31.12.2002

Remark	:	dose-group. The concentrations tested are not specified for the test materials in this publication (there are a large number) but it is noted that the dilution factor was initially 1:2 but if the result did not yield an EC0 and an EC100 with enough separation (three steps) that could be used to graphically determine the EC50, closer dilution factors (1.4 and 1.1) were used. No analytical data on the actual concentrations are provided. EC50 values were determined graphically from the actual EC0 and EC100.
	:	The data indicate a rather steep dose response relation for the test material. This increases the accuracy for the EC50 determination. The lack of analytical data for this somewhat volatile compound is a confounder; however, it is less important as the exposure time was only 24 hours.
Result	:	This study states a lower LC50 than the latter study by the same investigators. The conditions were similar except this study used tap water for the investigations and the later study use reconstituted fresh water in an attempt to standardize the conditions and improve repeatability.
	:	The 24-hour EC50 graphically determined for propargyl alcohol was 11 mg/L with an EC0 of 6.3 mg/L and an EC100 of 25 mg/L.
Test substance	:	Propargyl alcohol, CASNO 107-19-7
Reliability	:	(2) valid with restrictions Published article with good detail by reliable investigators.
30.12.2002		(8)

### 4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus quadricauda (Algae)
Endpoint	:	other: cell density
Exposure period	:	8 day(s)
Unit	:	mg/l
EC03	:	= 18
Limit test	:	no
Analytical monitoring	:	no
Method	:	Duplicate flasks containing 40 ml serially diluted test substance at a 1:1 ratio were inoculated with 5 ml concentrated (10X) media and 5 ml of a standardized concentration of algae. Flasks were incubated for 8 days at 27 deg under fluorescent lamps with shaking. After 8 days, relative concentration of cells was estimated by measuring the absorption and scattering of light at 578 nm from a mercury lamp. The measurement was conducted with a 10 mm light path cell after mixing the suspension to assure homogeneity.
Remark	:	The cell density was plotted graphically using semilog paper and the concentration that corresponded to a 3% reduction in cell density was determined and referred to as the "Toxiche Grenzkonzentration" or TGK. This translates into toxic threshold concentration in English. In the referenced report the TGK for about 200 substances was reported along with a TGK value for Pseudomonas putida. Because of the large volume of data, individual data for cell densities were not provided.
	:	This study has an impressive ammount of information and appears to have been well-conducted. Analytical verification of concentrations is missing

## 4. Ecotoxicity

Id 107-19-7

Date 31.12.2002

and this could be a factor for materials that lack water stability or are volatile. The high water solubility and relatively low volatility (Henry's Law constant) for Propargyl alcohol and its stability in water suggest that this test produced a reasonable estimate of the toxicity of the test material to green algae.

**Result** : The toxic threshold concentration for 8-day growth of *Scenedesmus quadricauda* was found to be 18 mg/L. The toxic threshold concentration for *Pseudomonas putida* was reported as 150mg/L

**Test substance** : Propargyl alcohol, CASNO 107-19-7

**Reliability** : (2) valid with restrictions  
Acceptable Publication, part of major study of similar compounds.

**Flag** : Critical study for SIDS endpoint  
30.12.2002 (10)

**Species** : other algae:Generic green for modeling

**Endpoint** : other: growth inhibition

**Exposure period** : 96 hour(s)

**Unit** : mg/l

**EC50 (SRC)** : = 17.7

**CE50 (CLOGP)** : = 117

**Method** : other: ECOSAR model

**Year** :

**GLP** :

**Test substance** :

**Method** : This estimate of the potential of Propargyl alcohol was made using the U.S.EPA-developed ECOSAR software. This software utilizes two different SAR equations to estimate the 96-hour growth inhibition of green algae. The first (SRC) was derived using the SRC software to estimate the Kow of the materials in the "training set" and the second used the CLOGP methodology. As this material has an experimentally determined Kow, it is preferred to use the true value in the estimate; thus there is no way to distinguish a preference for one equation of the other without additional information.

The SAR equations and limitations are:

$\text{Log GA 96-h EC50 (mmoles/L)} = -0.687 - 0.533 \log \text{Kow} \quad (\text{using ClogP})$   
where  $n_2$ ,  $R^2=1.0$ ,  $\log \text{Kow} < 6.4$ ,  $\text{MW} < 1000$

$\text{Log GA 96-h EC50 (mmoles/L)} = 0.091 - 0.655 \log \text{Kow} \quad (\text{using SRC Kowwin})$   
where  $n_2$ ,  $R^2=1.0$ ,  $\log \text{Kow} < 6.4$ ,  $\text{MW} < 1000$

These equations were used to make the estimate with the measured log Kow of -0.35 using ECOSAR version 0.99f

**Result** : Full output of the ECOSAR program

ECOSAR Program (v0.99f) Results:  
=====

SMILES : C#CCO  
CHEM : Propargyl Alcohol  
CAS Num:  
ChemID1:

## 4. Ecotoxicity

Id 107-19-7

Date 31.12.2002

ChemID2:  
ChemID3:  
MOL FOR: C3 H4 O1  
MOL WT : 56.06  
Log Kow: -0.35 (User entered)  
Melt Pt: -52.00 deg C  
Wat Sol: 1E+006 mg/L (measured)

### ECOSAR v0.99f Class(es) Found

-----  
Propargyl Alcohols

Predicted

ECOSAR Class	Organism	Duration	End Pt	mg/L (ppm)
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=====

Neutral Organic SAR:Fish		14-day	LC50	8385.703
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(Baseline Toxicity)

Propargyl Alcohols: Fish [CLOGP]	96-hr	LC50	4.669
Propargyl Alcohols: Fish [SRC]	96-hr	LC50	8.530
Propargyl Alcohols: Daphnid [CLOGP]	48-hr	LC50	4.630
Propargyl Alcohols: Daphnid [SRC]	48-hr	LC50	11.400
Propargyl Alcohols: Green Algae[CLOGP]	96-hr	EC50	17.711**
Propargyl Alcohols: Green Algae[SRC]	96-hr	EC50	117.203**
Propargyl Alcohols: Fish [CLOGP]	ChV		0.186
Propargyl Alcohols: Fish [SRC]	ChV		0.354
Propargyl Alcohols: Daphnid [CLOGP]	ChV		0.228
Propargyl Alcohols: Daphnid [SRC]	ChV		0.947
Propargyl Alcohols: Green Algae [CLOGP]	ChV		9.743
Propargyl Alcohols: Green Algae [SRC]	ChV		63.189

Test substance

:

Propargyl alcohol, CASNO 107-19-7

Reliability

:

(2) valid with restrictions

Calculated by an acceptable method using measured physicochemical parameters.

30.12.2002

(11)

### 4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

## 5. Toxicity

Id 107-19-7

Date 31.12.2002

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### 5.1.1 ACUTE ORAL TOXICITY

Type : LD50  
Value : = 55 - 110 mg/kg bw  
Species : rat  
Strain : Sprague-Dawley  
Sex : male/female  
Number of animals : 120  
Vehicle : water  
Doses :  
Method :  
Year :  
GLP : no data  
Test substance :

**Method** : Test substance in dosages ranging from 0 to 400 mg/kg in 0.5 ml aqueous solutions were administered by gavage to young adult male and females Sprague-Dawley weighing from 100 to 200 g. The treated animals were held 48 hours at 24°C with food and water *ad libitum*, after which the dead rats were counted. When treated, the females were 63 days old and the males were 46 days old. Propargyl alcohol was diluted with deionized water so that 0.5 ml contained the desired dosage. Animals were caged separately after gavage.

Four experiments were conducted to establish the LD50 for males and for females. Experiment I had 18 male and 18 female rats (two at each treatment level) treated at 0, 0.025, 0.050, 0.075, 0.100, 1.0, 10.0, 40.0, or 400 mg/kg and all rats survived except those treated at 400 mg/kg. In experiment II, 14 male and 14 female rats (two at each treatment level) were treated at 0, 100, 200, 250, 300, 350, or 400 mg/kg and all rats died except the controls. In experiment III there were 16 male and 16 female rats (two at each treatment level) treated at 0, 40, 50, 60, 70, 80, 90, or 100 mg/kg and all the female rats died at 60 mg/kg or higher and all remained alive from 0 through 50 mg/kg. All the male rats remained alive at all treatment levels. Experiment IV had 14 male rats (two at each treatment levels) treated at 0, 40, 80, 100, 110, 120, 150 or 200 mg/kg and all rats survived between 0 and 80, 1 died and 1 remained alive at 100 and 110 and all died at 120 mg/kg or higher doses.

The oral LD50 was calculated by the probit method (Finney, 1971).

**Result** : The oral LD50 was calculated by the probit method (Finney) as 110 (100-120) mg/kg for male rats and 55 (50-60) mg/kg for female rats.

Experimental animals that died had moderate multifocal medullary hemorrhage in the thymus, interstitial hemorrhage with atrophy of the surrounding acinar cells.

**Test substance** : Propargyl alcohol, CASNO 107-19-7 purity 97% (source: Aldrich Chemicals)

**Conclusion** : The oral LD50 was 110 (100-120) mg/kg for male rats and 55 (50-60) mg/kg for female rate.

**Reliability** : (1) valid without restriction  
Although no guideline was followed, the stated purpose was to clarify the

## 5. Toxicity

Id 107-19-7

Date 31.12.2002

oral LD50 of the test substance. The publication gives good detail and the study was conducted by a scientifically defensible method.	
<b>Flag</b> 30.12.2002	: Critical study for SIDS endpoint (2)
<b>Type</b>	: LD50
<b>Value</b>	: = 56 mg/kg bw
<b>Species</b>	: rat
<b>Strain</b>	: no data
<b>Sex</b>	: no data
<b>Number of animals</b>	:
<b>Vehicle</b>	: water
<b>Doses</b>	:
<b>Method</b>	: Study was conducted in accord with the standard laboratory procedure of that time as part of acute toxicity screen. The procedure is not specified except that the vehicle was distilled water and the test substance was administered as a 1% solution, the post-dosing observation period was 7 days, and the LD50 was calculated by the procedure of Litchfiels-Wilcoxon. Clinical signs were recorded and a necropsy was conducted but it is not specified if it was on all rats or only decedents.
<b>Remark</b>	: This result is in good agreement with other studies.
<b>Result</b>	: An oral LD50 of 56 mg/kg-bw was found with a confidence interval of 46.5 to 67.5. The strain, sex, age and weights of the test animals are not specified.  Clinical signs were reported as hyperactivity, accelerated respiration, prone position.  Necropsy findings were: Liver swelling in some individual rats, blood in intestine contents, bleeding in the lung.
<b>Test substance</b>	: Propargyl alcohol, CASNO 107-19-7
<b>Reliability</b>  30.12.2002	: (2) valid with restrictions Although some important details are missing, the original laboratory report was available and it provides sufficient detail to ascertain that the study was conducted using a scientifically defensible procedure. (4)
<b>Type</b>	: LD50
<b>Value</b>	: = 54 - 93 ml/kg bw
<b>Species</b>	: rat
<b>Strain</b>	: Sprague-Dawley
<b>Sex</b>	: male/female
<b>Number of animals</b>	:
<b>Vehicle</b>	:
<b>Doses</b>	:
<b>Method</b>	:
<b>Year</b>	:
<b>GLP</b>	: no data
<b>Test substance</b>	:
<b>Method</b>	: The method of Smyth et al. (Range-finding Toxicity data: List VI. Amer. Ind. Hyg. Ass. J. 23:95-107, 1962) was used to conduct this study. In the case of this material, enough data were collected to use the probit method

## 5. Toxicity

Id 107-19-7

Date 31.12.2002

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	(Finney, 1971) to calculate the LD50 values for each sex. Rats were Sprague-Dawley strain 200-300 grams.
Result	: Individual data are not provided in this report on the toxicity of about 100 materials. The data are in a table and for this test material the following oral data are given: a LD50 (males) of 93 mg/kg with a confidence interval of 58-150mg/kg and a LD50 (females) of 54 mg/kg with a confidence interval of 37-78.
Test substance	: Propargyl alcohol, CASNO 107-19-7
Conclusion	: The following LD50 were found under these conditions:  LD50 (males) of 93 mg/kg with a confidence interval of 58-150 mg/kg  LD50 (females) of 54 mg/kg with a confidence interval of 37-78 mg/kg
Reliability	: (2) valid with restrictions Published article in peer-reviewed journal.
31.12.2002	(29)

### 5.1.2 ACUTE INHALATION TOXICITY

Type	: LC50
Value	: = 1040 - 1200 ppm
Species	: rat
Strain	: Sprague-Dawley
Sex	: male/female
Number of animals	:
Vehicle	:
Doses	:
Exposure time	: 1 hour(s)
Method	:
Year	:
GLP	: no data
Test substance	:
Method	: Inhalation experiments were performed in bells jars or large desiccators using 5 rats per exposure level. One-hour LC50 were determined by the method of Thompson (1947, Bact. Rev. 11:115-145) and by Weil (1952, Biometrics 8:249-63). The chamber contaminant concentration was measured such that it gave a relative SD of 5% or less. In the case of this test material, there was enough test data to calculate the LC50 values using the probit procedure of Finney. Rats were Sprague-Dawley strain 200-300 grams.
Result	: Individual data are not provided in this report on the toxicity of about 100 materials. Data contained in the table for this test material regarding inhalation toxicity are: The 1-hour LC50 (males) is 1200 ppm with a confidence interval of 1180-1220ppm and the 1-hour LC50 (females) is 1040 ppm with a confidence interval of 970-1120 ppm.
Test substance	: Propargyl alcohol, CASNO 107-19-7
Conclusion	: The following 1-hour LC50 values were found under these conditions:  1-hour LC50 (rat, male) = 1,200 (1180-1220) ppm

## 5. Toxicity

Id 107-19-7

Date 31.12.2002

Reliability	: 1-hour LC50 (rat, female) = 1,040 (970-1120) ppm. : (2) valid with restrictions
30.12.2002	Published article in peer-reviewed journal. (29)
Type	: other: limit test, 1-hour exposure
Value	:
Species	: rat
Strain	: Sprague-Dawley
Sex	: male/female
Number of animals	: 10
Vehicle	:
Doses	: 1490 ppm
Exposure time	: 60 minute(s)
Method	:
Year	:
GLP	: yes
Test substance	:
Method	: Test animals were Sprague-Dawley (CrI:CD®BR) rats received from Charles River Laboratories, Inc., Raleigh, North Carolina. Animals were acclimated to laboratory conditions for one week prior to treatment.  Exposure of the test animals was conducted in a 100 liter plexiglass chamber. The chamber was operated in a dynamic mode with total airflow through the chamber of 19.2 liters per minute (lpm) as measured using a calibrated flowmeter.  The test material was used as received and was generated as a vapor in the breathing zone of the animals using tandem bubblers. House air was metered through a valve, a 0-30 lpm Dwyer flowmeter, and a backpressure gauge to the 500 ml fritted disk gas wash bottle via I.D. Tygon tubing. Additional Tygon tubing connected the first 500 ml fritted disk gas wash bottle with the second 500 ml fritted disk gas wash bottle. Both bubblers were filled to approximately 20-25% capacity with test article. Additional Tygon tubing connected the second 500 ml fritted disk gas wash bottle to a 500 ml 3-necked flask containing glass wool. The flask was connected to the 100 liter exposure chamber with a glass adapter and stopper. Dilution air was metered to the 3-necked flask through a valve, a 0-20 lpm Dwyer flowmeter, and a backpressure gauge via Tygon tubing.  After 60 minutes of exposure, the test material generation system was turned off and compressed air was passed through the exposure chamber at the same rate for an additional half-hour to clear residual propargyl alcohol vapor. At 30 minutes post-exposure, the chamber was opened and the animals were removed.  Animals were observed every 15 minutes during the exposure. Physical examinations were performed prior to exposure, at removal from the chamber 60 minutes after the end of exposure, and once daily thereafter. Animals were examined at least twice daily for mortality and moribundity. Animals were weighed just prior to exposure and at death. All animals found dead were subjected to a complete postmortem examination. No tissues were saved
Result	:

## 5. Toxicity

Id 107-19-7

Date 31.12.2002

The mean (time weighted average) exposure level of propargyl alcohol was determined by MIRAN assay to be  $1490 \pm 159.8$  ppm. Particle size distribution measurements revealed the test atmosphere contained only a vapor. Clinical signs associated with treatment included hunched posture, rough hair coat, increased secretory responses, low body temperature, languid behavior, prostration, and death. All animals died by Test Day 3. Gross postmortem evaluations revealed numerous findings, all of which were ascribed to post-mortem changes. There were no lesions which were obviously related to treatment.

**Test substance** : Propargyl alcohol, CASNO 107-19-7  
**Reliability** : (1) valid without restriction  
Guideline-like study under GLPs with good documentation.  
30.12.2002 (18)

### 5.1.3 ACUTE DERMAL TOXICITY

**Type** : LD50  
**Value** : = 88 mg/kg bw  
**Species** : rabbit  
**Strain** : New Zealand white  
**Sex** : female  
**Number of animals** :  
**Vehicle** :  
**Doses** :  
**Method** : other: Smyth (1962)  
**Year** :  
**GLP** :  
**Test substance** :

**Method** : The method of Smyth et al. (Range-finding Toxicity data: List VI. Amer. Ind. Hyg. Ass. J. 23:95-107, 1962) was used to conduct this study except that three female rabbits were used per dose and the dosed were kept in place by 8-ply gauze patches under a rubber latex film. The LD50 was determined using the moving average method as described by Thompson (1947, Bact. Rev. 11:115-145) and by Weil (1952, Biometrics 8:249-63).

**Result** : Rabbits were females 3-4 kg  
Individual data are not provided in this report of the toxicity of about 100 materials. The data are in a table and for this test material; a dermal LD50 of 88 mg/kg body weight is reported

**Test substance** : Propargyl alcohol, CASNO 107-19-7  
**Reliability** : (2) valid with restrictions  
Published article in peer-reviewed journal.  
**Flag** : Critical study for SIDS endpoint  
30.12.2002

**Type** : LDLo  
**Value** : ca. 15 mg/kg bw  
**Species** : rabbit  
**Strain** :  
**Sex** :  
**Number of animals** :  
**Vehicle** :

## 5. Toxicity

Id 107-19-7

Date 31.12.2002

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Doses	:	
Method	:	
Year	:	
GLP	:	no
Test substance	:	
Method	:	Few details are given in this short report. Material was administered as a 1.58% solution in Dowanol 50B and remained on the skin of rabbits for 24 hours. There were two rabbits per test group and three test groups at 7.95, 15.8 and 31.6 mg/kg-bw. Mortality in the test groups was 0/2, 1/2 and 1/2, respectively. Observation time not reported.
Remark	:	<p>Clinical signs were reported at the two higher doses and consisted of slight diarrhea, hyperemia and moderate edema.</p> <p>This study is usefull in confirming the high-degree of dermal toxicity for this material and demonstrating that the dermal toxicity is probably enhanced by solvents that increase dermal absorption. The Dermal LD50, using water as vehicle, for comparison is 88 mg/kg-bw.</p> <p>Dowanol-50 is listed in the literature as Dipropyleneglycol monomethyl ether.</p>
Test substance	:	Propargyl alcohol, CASNO 107-19-7
Conclusion	:	The LDlo for this material as a Dowanol-50 solution in the rabbit is 15 mg/kg-bw.
Reliability	:	(2) valid with restrictions Although details are lacking, original report was available.
30.12.2002		(24)

### 5.1.4 ACUTE TOXICITY, OTHER ROUTES

### 5.4 REPEATED DOSE TOXICITY

Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	inhalation
Exposure period	:	90-days
Frequency of treatm.	:	daily
Post exposure period	:	
Doses	:	0, 2, 4, 8, 16 and 32 ppm
Control group	:	
NOAEL	:	= 16 ppm
LOAEL	:	= 32 ppm
Method	:	other: NTP SOW
Year	:	
GLP	:	yes
Test substance	:	
Method	:	Male and female F344 rats (20/sex/group; 10 allocated to the core study and 10 allocated for clinical pathology testing) were exposed by whole-

## 5. Toxicity

Id 107-19-7

Date 31.12.2002

body inhalation to target concentrations of 0, 4, 8, 16, 32, or 64 ppm propargyl alcohol for up to 13 weeks.

This was conducted by developing a system to generate, deliver, and monitor concentrations of test material vapor for inhalation exposures in whole body exposure chambers. During the study, measurements were made to validate the performance of the exposure generation and monitoring system. The test atmosphere concentrations and environmental conditions during the study were within the protocol-specified range for daily means for all exposures. In addition, studies were conducted demonstrating that propargyl alcohol was stable under the generation and exposure conditions and the uniformity in the exposure chambers was acceptable.

### Result

Results of the study in rats are summarized below

#### EFFECTS MALE RATS

Mortality and 13-week body weights

	Exposure Concentration (ppm)					
	0	4	8	16	32	64
Mortality	0/10	0/10	0/10	0/10	0/10	0/10
Body wt [g]	334.6	353.9	333.3	336.5	332.0	327.7
± SD	±13.6	± 22.1	±28.4	±29.0	±8.4	±23.2
%Difference	NA	+5.8	-0.4	+0.6	-0.8	-2.1

#### Necropsy Findings

	Exposure Conc (ppm)					
	0	4	8	16	32	64
Gross observations	NS	NS	NS	NS	NS	NS
Increased kidney/body wt	NA	NS	NS	NS	NS	++
Increased liver weight	NA	NS	NS	NS	NS	++
Increased liver/body wt	NA	NS	NS	NS	++	++

#### Clinical Pathology Findings

	Exposure Conc (ppm)					
	0	4	8	16	32	64
Day 3: Increased BUN	NA	NS	NS	NS	++	++
Day 23: Increased BUN	NA	NS	NS	NS	+	++
Day 23: Decreased cholin'ase	NA	NS	NS	NS	NS	+
SAC: Decreased cholinest'ase	NA	NS	NS	NS	+	++

#### Histopathology

	Exposure Conc (ppm)					
	0	4	8	16	32	64
Necrosis, olfactory epithelium, nose	0/10	0/10	0/10	0/10	2/10	5/10
Hyperplasia, respiratory epithelium nose	2/10	6/10	2/10	4/10	8/10	10/10
Squamous metaplasia respiratory epithelium nose	0/10	0/10	0/10	0/10	0/10	3/10

+ = Sig at < 0.05

++ = Sig at < 0.01

## 5. Toxicity

Id 107-19-7

Date 31.12.2002

### EFFECTS FEMALE RATS Mortality and 13-week body weights

	Exposure Concentration (ppm)					
	0	4	8	16	32	64
Mortality	0/10	0/10	0/10	0/10	0/10	0/10
Body wt [g]	195.9	203.6	190.2	190.7	197.0	190.0
± SD	±14.1	±18.4	±12.7	±12.1	±10.3	±9.5
%Difference	NA	+3.9	-2.9	-2.7	+0.6	-3.0

Necropsy Findings	Exposure Conc (ppm)					
	0	4	8	16	32	64
Gross observations	NS	NS	NS	NS	NS	NS
Increased kidney/body wt	NA	NS	NS	NS	NS	++
Increased liver/body wt	NA	NS	NS	NS	NS	++

Clinical Pathology Findings	Exposure Conc (ppm)					
	0	4	8	16	32	64
Day 3: Increased BUN	NA	NS	NS	NS	++	++
Day 3: Decreased cholin'ase	NA	NS	NS	NS	++	+
Day 23: Decreased cholin'ase	NA	NS	NS	+	++	++
SAC: Decreased cholinest'ase	NA	NS	+	+	++	++

Histopathology	Exposure Conc (ppm)					
	0	4	8	16	32	64
Necrosis, olfactory epithelium, nose	0/10	0/10	0/10	0/10	3/10	5/10
Hyperplasia, respirat epithe'm nose	0/10	2/10	2/10	2/10	10/10	10/10
Squamous metaplasia respiratory epit'm nose	0/10	0/10	0/10	0/10	0/10	8/10
Necrosis respiratory epit'm nose	0/10	0/10	0/10	0/10	0/10	2/10
+ = Sig at < 0.05						
++ = Sig at < 0.01						

Exposure did not result in any significant in-life toxic effects, except for lesions in the nasal cavity and depressed serum cholinesterase levels in both sexes. Survival was 100% for all groups and there was no significant effect of exposure on body weight or weight gain in males or females. Clinical signs were unremarkable; there were no changes in hematology parameters. At exposures of = 32 and = 8 ppm for males and females, respectively; serum cholinesterase levels were depressed initially and remained depressed until terminal sacrifice. This was particularly manifest in females, increasing progressively with increasing exposure concentrations and involving lower concentrations as exposures progressed.

Gross lesions related to treatment were not observed. Relative kidney and liver weights were significantly increased at 64 ppm in rats of each sex. Adverse effects on the kidney were indicated by elevated BUN levels at 32 and 64 ppm early in the study. Relative lung weights were elevated in males exposed to 64 ppm. Significant exposure-related histopathology findings were limited to the nose in males and females. A no-effect level

## 5. Toxicity

Id 107-19-7

Date 31.12.2002

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	could not be determined because of hyperplasia of the respiratory epithelium in both sexes. Metaplasia in the nose occurred in male and female rats at the high concentration. Necrosis of the olfactory epithelium was observed in males and females exposed at 32 or 64 ppm, while necrosis of the respiratory epithelium was limited to the 64-ppm females. A no-effect level based on these observations (necrosis and metaplasia) was 16 ppm.
<b>Test substance</b>	: Propargyl alcohol, CASNO 107-19-7, purity >99.6%
<b>Reliability</b>	: (1) valid without restriction NTP Guideline study under GLP with full QA reviews
<b>Flag</b> 30.12.2002	: Critical study for SIDS endpoint (22)
<b>Type</b>	: Sub-chronic
<b>Species</b>	: rat
<b>Sex</b>	:
<b>Strain</b>	: Wistar
<b>Route of admin.</b>	: inhalation
<b>Exposure period</b>	: 90-days
<b>Frequency of treatm.</b>	: daily, except weekends
<b>Post exposure period</b>	: none
<b>Doses</b>	: 1.1, 5.1 and 24.6 ppm
<b>Control group</b>	: yes, concurrent vehicle
<b>NOAEL</b>	: = 5.1 ppm
<b>LOAEL</b>	: = 24.6 ppm
<b>Method</b>	:
<b>Year</b>	:
<b>GLP</b>	: yes
<b>Test substance</b>	:
<b>Method</b>	: Propargyl alcohol vapor was tested for its inhalation toxicity in Wistar rats. 10 female and 10 male rats per group were exposed to target concentrations of 25 ppm, 5 ppm and 1 ppm on 6 hours/day, 5 days/week for a period of 90 days (65 exposures). A control group of 10 female and 10 male rats inhaled clean air under similar exposure conditions. Body weights of the animals were determined weekly during the exposure period. Clinical signs and findings were recorded on exposure days. Mortality was checked daily.
<b>Remark</b>	: As this is only a supporting study, details are kept to a minimum.
<b>Result</b>	: Mean measured vapor concentrations were very close to target at 1.1, 11.4 and 24.6 ppm. No mortality was recorded and there were not any treatment-related clinical signs reported. Body-weight gains were statistically unaffected at the end of the study; however, male rats showed statistically significant reduction in body weight-gain during the first 2 weeks of exposure.  In females of the high-dose group, absolute and relative kidney weights were increased and cholinesterase activity was decreased.  Complete histopathologic examination found no treatment related organ effects.  Clinical chemistry and hematology results were unremarkable.
<b>Test substance</b>	:

## 5. Toxicity

Id 107-19-7

Date 31.12.2002

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Reliability	: Propargyl alcohol, CASNO 107-19-7, purity 99.4%
	: (1) valid without restriction
	: Guideline-like study under GLPs with good documentation.
31.12.2002	(3)
Type	: Sub-chronic
Species	: rat
Sex	: male/female
Strain	: Sprague-Dawley
Route of admin.	: gavage
Exposure period	: 13 Weeks
Frequency of treatm.	: daily
Post exposure period	: none
Doses	: 5, 15, 50 mg/kg-day
Control group	: yes, concurrent vehicle
NOAEL	: = 5 mg/kg bw
LOAEL	: = 15 mg/kg bw
Method	:
Year	:
GLP	: yes
Test substance	:

**Method** : Four groups of rats (30/sex/group) were dosed orally once daily with 0, 5, 15, or 50 mg/kg of propargyl alcohol. Animals were Crl:CD (SD)BR rats obtained from the Portage Michigan facility of Charles River Laboratories and were 45-50 days old at the start of treatment. The first ten rats of each group were scheduled for the interim sacrifice after dosing for 4-weeks. The remaining 20 rats in each group were scheduled for the final sacrifice after dosing for 91 or 92 days. A fifth group of 10 males and 10 females were sacrificed before initiation of dosing for baseline clinical pathology data.

Samples of gavage solutions were tested at intervals during the study to assure the proper quantity of test material was administered.

Body weights and food consumption were recorded weekly. Observations for mortality and/or overt signs of toxicity were made four times daily. Ophthalmologic examinations were performed during the pretreatment period and again during week 13. Blood for clinical pathology evaluation was collected from all surviving rats scheduled for the interim sacrifice on week-4, and from the first ten surviving rats/sex/group (except high-dose males) at the final sacrifice. The first ten rats of each sex from each group were sacrificed on day 29 or 30 (except only nine high-dose males). All remaining surviving rats were sacrificed on day 92 or 93. Gross postmortem examinations were done on all treated and control animals. Organ weights were recorded at terminal sacrifice. A complete histopathologic examination was done on all rats sacrificed at the end of the study in the control and the high-dose groups; on livers, kidneys, and lungs from the rats in the 5 and 15 mg/kg/day dose groups; the livers from rats necropsied at the interim sacrifice and on all gross lesions. In addition, a complete histopathologic examination was conducted on all rats found dead.

**STATISTICAL METHODS** The data were tested for homogeneity of variance by Bartlett's method (Snedecor and Cochran, 1967). If the data were found to be homogeneous, differences between control and treatment means were tested for statistical significance by the method of Dunnett

### Result

(Dunnett, 1964). If the data were found not to be homogeneous, the method of Gill (modified Dunnett's) was employed (Gill, 1977).

#### EFFECTS AFTER FOUR WEEKS

Effects during the first four weeks of the study the effects were:

- (1) Death of one male in the 50 mg/kg/day dose group
- (2) An increasing incidence of salivation in the 50 mg/kg/day dose group
- (3) Significantly lower body weights in the high-dose males and a similar trend in the females
- (4) A trend toward higher food consumption in the high-dose males that was statistically significant in week 3
- (5) Reduced hemoglobin and mean corpuscular hemoglobin in high-dose females and in the high-dose males, lower mean corpuscular volume.
- (6) Increased total leucocyte and absolute neutrophil count for the high-dose males,
- (7) Higher than normal values in two high-dose males and one high-dose female for the SGOT, SGPT and LDH
- (8) Reduced serum glucose and sodium in the high-dose males
- (9) Mottling and light or dark areas in the livers of some high-dose males
- (10) Histologically, megalocytosis of hepatocytes in both sexes of the 15 and 50 mg/kg/day dose groups.

#### EFFECTS AFTER 13-WEEKS

After 13-weeks, four males from the high-dose dose group had died. Salivation was the most prevalent treatment-related clinical sign, occurring predominately prior to dosing in the high-dose dose group.

**BODY WEIGHTS** Body weights of high-dose males were 16% lower ( $p < 0.01$ ) than controls and high-dose females were 9% (not significant) lower. There was a tendency toward increased food consumption in the mid and high-dose groups.

No treatment-related effect was observed upon ophthalmoscopic examination.

**HEMATOLOGY** High-dose males had reduced hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration. High-dose females showed reduced mean corpuscular volume and mean corpuscular hemoglobin. In addition, the absolute neutrophil count was higher in mid and high-dose males.

**CHEMISTRY** High-dose males and females had increased SGOT, SGPT and Alk Phos. Serum glucose and sodium concentrations were lower than controls for high-dose males. Serum cholesterol was reduced in high-dose males compared to controls. Serum albumin and globulin in the males and globulin in the females was lower for the high-dose group. Serum creatinine levels were lower than controls for high dose males and females.

**ORGAN WEIGHTS** Absolute and relative liver weights of mid and high-dose males and females were greater than controls. In the low dose males and females, the absolute and relative liver weights of both sexes were higher than controls but not significantly so. Absolute kidney weights of mid and high-dose females and the relative kidney weights of high-dose males were increased.

## 5. Toxicity

Id 107-19-7

Date 31.12.2002

**HISTOPATHOLOGY** Liver and kidneys were the most affected organs. The predominant hepatic lesion was megalocytosis of hepatocytes with a less prominent proliferation of the bile ducts and hepatocytic cytoplasmic vacuolation. This occurred in all high-dose rats treated for one or three months, in all mid-dose rats treated for thirteen weeks and in 9/10 mid-dose males and 5/10 mid-dose females treated for four weeks. In the low-dose group hepatocytic megalocytosis was seen in one rat treated for thirteen weeks. The most prevalent renal lesion was karyomegaly (enlarged nuclei) of renal tubular epithelial cells. The incidence and grade of renal karyomegaly showed a dose response effect, occurring in the mid and high-dose groups of males and in the high-dose females. The low-dose group dose group was not affected.

<b>Test substance</b>	:	Propargyl alcohol, CASNO 107-19-7, purity >99%
<b>Conclusion</b>	:	Administration of 15 or 50 mg/kg-day of Propargyl alcohol to rats for 13-weeks was associated with significant adverse effects on the liver and kidneys at 50 mg/kg and potentially adverse effects seen by histopathology at 15 mg/kg-day. The 50 mg/kg-day dose in males also was associated with reduced body weight gain, 20% mortality and reduction in hemoglobin, mean corpuscular volume and corpuscular hemoglobin. The low-dose, 5 mg/kg-day, was a NOAEL.
<b>Reliability</b>	:	(1) valid without restriction Guideline-like study under GLPs with good documentation. Full report available for review.
<b>Flag</b> 30.12.2002	:	Critical study for SIDS endpoint (27)
<b>Type</b>	:	Sub-chronic
<b>Species</b>	:	mouse
<b>Sex</b>	:	male/female
<b>Strain</b>	:	B6C3F1
<b>Route of admin.</b>	:	inhalation
<b>Exposure period</b>	:	13-weeks
<b>Frequency of treatm.</b>	:	daily
<b>Post exposure period</b>	:	
<b>Doses</b>	:	0, 2, 4, 8, 16 and 32 ppm
<b>Control group</b>	:	
<b>NOAEL</b>	:	= 8 ppm
<b>LOAEL</b>	:	= 16 ppm
<b>Method</b>	:	other: NTP SOW
<b>Year</b>	:	
<b>GLP</b>	:	yes
<b>Test substance</b>	:	
<b>Method</b>	:	Male and female B6C3F1 (10/sex/group) were exposed by whole-body inhalation to target concentrations of 0, 4, 8, 16, 32, or 64 ppm propargyl alcohol for up to 13 weeks.
<b>Result</b>	:	Results of the study in mice are summarized below

## 5. Toxicity

Id 107-19-7

Date 31.12.2002

### EFFECTS MALE MICE

Mortality and 13-week body weights

	Exposure Concentration (ppm)					
	0	4	8	16	32	64
Mortality	0/10	0/10	0/10	0/10	0/10	0/10
Abnor Bre'ing	0/10	0/10	0/10	0/10	0/10	8/10
Body wt [g]	39.8	38.6	37.9	36.4*	35.3*	33.6*
± SD	±2.7	±1.3	±2.4	±2.9	±2.1	±1.6
% Difference	NA	-2.9	-4.7	-8.5	-11.3	-15.6

### Necropsy Findings

	Exposure Conc (ppm)					
	0	4	8	16	32	64
Gross observations	NS	NS	NS	NS	NS	NS
Increased kidney/body wt	NA	NS	+	++	++	++
Increased liver/body wt	NA	NS	NS	+	+	++

### Clinical Pathology Findings

	Exposure Conc (ppm)					
	0	4	8	16	32	64
Decreased RBCs	NA	NS	NS	NS	+	++
Decreased Hb	NA	NS	NS	NS	++	++
Decreased PCV	NA	NS	NS	NS	++	++

### Histopathology

	Exposure Conc (ppm)					
	0	4	8	16	32	64
Inflammation, nose	0/10	0/10	0/10	0/10	0/10	6/10
Hyperplasia glands, nose	0/10	0/10	0/10	3/10	9/10	9/10
Necrosis, olfactory epithelium, nose	0/10	0/10	1/10	0/10	1/10	0/10
Atrophy, olfactory epithelium, nose	0/10	0/10	0/10	0/10	8/10	10/10
Hyaline Degeneration resp'tory epit'm nose	0/10	0/10	0/10	0/10	3/10	9/10
Squamous metaplasia resp'tory epit'm nose	0/10	0/10	0/10	0/10	5/10	10/10

+ = Sig at < 0.05

++ = Sig at < 0.01

### EFFECTS FEMALE MICE

Mortality and 13-week body weights

	Exposure Concentration (ppm)					
	0	4	8	16	32	64
Mortality	0/10	0/10	0/10	0/10	0/10	0/10
Abnor Bre'ing	0/10	0/10	0/10	0/10	0/10	10/10
Body wt [g]	31.8	32.0	31.2	31.3	29.6	28.1*
± SD	±2.7	±2.4	±3.5	±3.3	±1.2	±1.4
% Difference	NA	+0.8	-2.0	-1.5	-7.0	-11.7

## 5. Toxicity

Id 107-19-7

Date 31.12.2002

Necropsy Findings	Exposure Conc (ppm)					
	0	4	8	16	32	64
Gross observations	NS	NS	NS	NS	NS	NS
Increased kidney/body wt	NA	NS	NS	NS	++	++

Histopathology	Exposure Conc (ppm)					
	0	4	8	16	32	64
Inflammation, nose	0/10	0/10	0/10	0/10	1/10	10/10
Hyperplasia glands, nose	0/10	0/10	0/10	0/10	8/10	10/10
Necrosis, olfactory epithelium, nose	0/10	0/10	0/10	9/10	4/10	0/10
Atrophy, olfactory epithelium, nose	0/10	0/10	0/10	0/10	7/10	10/10
Hyaline Degeneration resp'tory epit'm nose	0/10	0/10	0/10	0/10	7/10	8/10
Squamous metaplasia resp'tory epit'm nose	0/10	0/10	0/10	1/10	7/10	10/10
+ = Sig at < 0.05						
++ = Sig at < 0.01						

Propargyl alcohol exposure for 13 weeks induced significantly depressed body weights among 16-ppm and higher level male mice and 64-ppm female mice. The 64-ppm mice showed signs of abnormal breathing on Days 8 and 9. A mild nonregenerative anemia was reported in males after 13 weeks of exposure to 32 or 64 ppm. Liver to body weight ratios were elevated in males exposed at 16 ppm and higher. Relative kidney weights were also elevated among males exposed at 8 ppm and higher, and females exposed at 32 or 64 ppm. Although all these organ weight changes were significant, they were confounded by concomitant propargyl alcohol effects involving body weight reduction. Overall, these results indicate that males were more sensitive to the toxic effects of the test material.

No gross lesions related to exposure were observed at necropsy. Significant histopathology findings occurred only in the nose. All nasal lesions, except for necrosis of the olfactory epithelium, were clearly exposure-related. Inflammation was restricted to the 64-ppm exposure level, except for a single 32-ppm female. Excluding the single observation of necrosis of the olfactory epithelium in a 8-ppm male, a no-effect level of 8 ppm could be determined.

<b>Test substance</b>	:	Propargyl alcohol, CASNO 107-19-7, purity >99.6%	
<b>Reliability</b>	:	(1) valid without restriction	
<b>Flag</b>	:	NTP Guideline study under GLP with full QA reviews	
30.12.2002	:	Critical study for SIDS endpoint	(22)
<b>Type</b>	:	Sub-chronic	
<b>Species</b>	:	rabbit	
<b>Sex</b>	:	male/female	
<b>Strain</b>	:	no data	
<b>Route of admin.</b>	:	dermal	
<b>Exposure period</b>	:	90 days	

## 5. Toxicity

**Id** 107-19-7

**Date** 31.12.2002

**Frequency of treatm.** : daily, except weekends  
**Post exposure period** :  
**Doses** : 1, 3, 10 (20) mg/kg-bw  
**Control group** : yes, concurrent vehicle  
**NOAEL** : = 13.3 mg/kg bw  
**Method** :  
**Year** : 1965  
**GLP** : no  
**Test substance** :

**Method** : Thirty-six albino rabbits (2-3 kg) were obtained and observed for a period of two weeks to assure health. The animals were then divided into four groups.

Control,	10 animals, 5 each sex;
1 mg/kg-day,	8 animals, 4 each sex
3 mg/kg-day,	8 animals, 4 each sex
10 (20) mg/kg-day,	10 animals, 5 each sex

In each group, half the animals of each sex were exposed with intact skin and half with abraded skin. The test material was applied as w/v solutions in distilled water using 1.0%, 0.3% and 0.1% for high to low groups respectively. Beginning on the 63rd day the daily dosage applied to high-dose animals was doubled, using a 2.0% solution. All dosages were applied in four equal increments, equally spaced through the day, five days per week. All animals were confined throughout each 8-hour exposure day. Control animals were handled in a manner similar to the test animals with distilled water applied four times daily.

Animals were weighed twice weekly during the first four weeks of the study and weekly thereafter, and doses were adjusted. Hematology (hemoglobin, red blood cell count, white blood cell count, differential count) was performed prior to the experiment, at 45-days and at termination. Determination of alkaline phosphatase, blood urea nitrogen (BUN) and serum glutamic pyruvic transaminase (SGPT) were performed prior to the start of the experiment, at 14-days and at 80-days.

At termination each animal was given a complete gross necropsy and organ weights of liver, kidney, Brain, adrenal, heart, spleen, stomach, testis (m), ovary (f) were recorded.

Sections of several organs were fixed, section and examined microscopically in controls and high-dose animals. These were: Brain, adrenal, heart, spleen, stomach, small intestine, pancreas, liver, kidney, gonads and skin.

**Remark** : This study has a high level of documentation available with individual animal data for body weights, hematology, and pathology being presented. Summary tables are not included nor is any description of the statistical methods. With the small numbers of animals and without statistical evaluation a firm conclusion cannot be drawn concerning minor systemic effects. The histopathological evaluations on the high-dose animals are valuable and demonstrate lack of specific organ toxicity under these conditions.

**Result** : The dosing regime of 4 doses/day is unusual.

## 5. Toxicity

Id 107-19-7

Date 31.12.2002

No deaths occurred during the study. Analysis of the weight changes shows that there were no patterns of response attributable to the dosages applied. Neither the sex of the animals nor the condition of the skin at application (abraded or intact) appears to have any significant effect upon the experimental animals' weight changes as compared to those of the control animals

No significant treatment-related observations were made upon gross examination of the animals at necropsy. No significant treatment-related differences between tissues from control and treated rabbits were found.

Analysis of the values obtained for alkaline phosphatase, BUN, and SGPT shows there to be no significant difference between any of the experimental groups as compared to the control group.

Hematological findings in the experimental animals did not differ significantly from those of the control animals. All were within the normal limits for the species.

<b>Test substance</b>	:	Propargyl alcohol, CASNO 107-19-7
<b>Conclusion</b>	:	Application of Propargyl Alcohol to the intact or abraded skin of young adult rabbits in daily doses of up to 10 mg/kg over a 63-day period and up to 20 mg/kg over a 28-day period produced no systemic effects.
<b>Reliability</b>	:	(4) not assignable

30.12.2002 (20)

### 5.5 GENETIC TOXICITY 'IN VITRO'

<b>Type</b>	:	Ames test
<b>System of testing</b>	:	S. typhimurium
<b>Test concentration</b>	:	4 to 2500 micrograms per plate
<b>Cycotoxic concentr.</b>	:	2500 mcg/plt without S9, 500 mcg/plt with S9
<b>Metabolic activation</b>	:	with and without
<b>Result</b>	:	negative
<b>Method</b>	:	
<b>Year</b>	:	
<b>GLP</b>	:	
<b>Test substance</b>	:	

**Method** : S. typhimurium strains TA1535, TA1538, TA100, TA1537, TA98 were tested using a plate incorporation technique both with and without metabolic activation. Aroclor 1254 induced rat liver S-9 was used for metabolic activation at a rate of 0.5 ml S-9 per plate when used with the overlay procedure. Test and control materials were incorporated directly into the overlay agar with the bacteria.

Plates were prepared and read in quadruplicate and a confirmatory assay was conducted to add additional dose levels).

Concentrations of test substance were tested from 4 to 2500 micrograms per plate with up to 7 different concentrations. The second study expanded the concentration range that was tested.

Statistical Methods

## 5. Toxicity

Id 107-19-7

Date 31.12.2002

		Formal statistical methods were not used to evaluate the data. Evaluations considered if a dose-response was observed and the magnitude of any increase in revertants..
Result	:	<p>In the initial study it was determined that the test material was slightly toxic to the test strains at 2500 micrograms/plate in the absence of S9. In the presence of S9, however, the test material displayed toxicity at levels of 500 microgram and above.</p> <p>The results of the initial and independent assays conducted on the test material at dose levels ranging from 4 to 2500 micrograms per plate in the absence and presence of metabolic activation did not exhibit increased numbers of his+ revertant colonies.</p> <p>The positive control treatments (without S9: MMNG, TA1535, TA1538, TA98 and TA100; 9-Aminoacridinumchloride, TA1537. with S9: Cyclophosphamide, TA1537, TA100; 2-Aminoanthrecene, TA1535, TA1537, TA1538, TA98 and TA100) in both the nonactivation and S9 activation assays induced large increases in the revertant numbers with all indicator strains, which demonstrated the effectiveness of the S9 activation system and the ability of the test system to detect known mutagens.</p>
Test substance	:	Propargyl alcohol, CASNO 107-19-7, purity ca. 99%
Conclusion	:	The test material, Propargyl alcohol, did not exhibit genetic activity in any of the assays conducted in this evaluation and was not mutagenic to the Salmonella typhimurium indicator organisms under the test conditions.
Reliability	:	(1) valid without restriction Guideline-like study with good documentation.
Flag	:	Critical study for SIDS endpoint
30.12.2002		
Type	:	Ames test
System of testing	:	
Test concentration	:	
Cycotoxic concentr.	:	0.75 mcl/plate
Metabolic activation	:	with and without
Result	:	negative
Method	:	
Year	:	
GLP	:	no data
Test substance	:	
Method	:	<p>The 3 chemicals were tested for reverse mutation in Salmonella strains TA97, TA98, TA100 and TA102 both with and without metabolic activation using Aroclor-induced Sprague-Dawley rat liver S9 mix (Moron and Ames, 1983). To avoid artifactual results due to test chemical-solvent interactions, each chemical was tested using at least 2 solvents.</p> <p>Tester strains used were TA97, TA98, TA100 and TA102. Five dose levels between 0.0075 and 0.75 mcl/plate were used to expose bacteria with and without S9 mix. The highest dose produce signs of toxicity in at least one strain. The test was run twice, once with DMSO as solvent and once with water as solvent.</p>

Data from the Salmonella/mammalian microsome assay were analyzed

## 5. Toxicity

Id 107-19-7

Date 31.12.2002

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**Result** : using the Salanal computer program developed by Integrated Laboratory Systems.

**Test substance** : Although the highest dose tested was sufficient to show signs of toxicity in at least one strain, The test material did not induce a reproducible, statistically-significant, dose-related increase in reverse mutations in any of the strains tested.

**Reliability** : Propargyl alcohol, CASNO 107-19-7 purity 97% (source: Aldrich Chemicals)

30.12.2002 : (2) valid with restrictions  
Acceptable Publication (12)

**Type** : Chromosomal aberration test

**System of testing** : CHO Cells

**Test concentration** : 0.4 to 10.0 mM

**Cycotoxic concentr.** :

**Metabolic activation** : with and without

**Result** : positive

**Method** :

**Year** :

**GLP** : no data

**Test substance** :

**Method** : Cell culture. Wild-type Chinese hamster ovary (CHO) cells were maintained in Eagle MEM supplemented with 1% sodium pyruvate, 1% non-essential amino acids and 10% fetal calf serum; (complete medium; all Gibco, Burlington, Ont.) at 37°C, 5% CO<sub>2</sub> and high humidity.

**Treatment.** 20000 CHO cells were added to 5 ml complete medium in 60-mm culture dishes and incubated as above overnight. For treatment, the complete medium was replaced with 1.4 ml treatment medium consisting of the test chemical diluted in either serum-free complete medium or an exogenous metabolic activation medium prepared as follows: 82% serum-free complete medium; 5.4% 20 mM HEPES buffer pH 7.2; 0.2% 0.5 M MgCl<sub>2</sub>; 0.2% 3.3 M KCl; 2% 40 mM NADP; 2% 50 mM glucose 6-phosphate; and 7% Aroclor 1254-induced rat-liver homogenate (S9). Vehicle controls were treated with treatment medium without the test chemical. The positive control was either 1 mM methyl methanesulfonate 5 mcg/ml mitomycin C for tests without metabolic activation and 25 mcg/ml cyclophosphamide for tests with metabolic activation. The cells were treated for 1 h then washed 3 times with Earle's balanced salt solution and incubated as above in 5 ml complete medium for 10 or 16 hr. Colcemid was added to all cultures for the final 2 hr of incubation. The cells were then scraped from the dishes using a rubber spatula, centrifuged at 1000 rpm for 5 min, resuspended in hypotonic 0.075 M KCl for 12 min at 37°C, centrifuged as above then resuspended in 3:1 ethanol-acetic acid. Chromosome preparations were made using standard cytological techniques then stained with 4% Giemsa (Gun R66 improved). 100 metaphase cells were scored from each of two cultures for each treatment. The slides were coded and scored blind to avoid observer bias.

Chromosomal aberration were analysed using Chromosomal Aberration Assay Data Management and Analysis System (Version 1.4) and the Micronucleus Assay Data Management and Analysis System (Version 1.4) developed under contract to the U.S. Environmental Protection Agency

## 5. Toxicity

Id 107-19-7

Date 31.12.2002

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		(Pellom et al., 1990). The criteria for a positive response were: a statistically significant, dose-related increase; and at least one dose that is statistically different from the solvent control.
Result	:	In cells collected 16 h following treatment, Propargyl alcohol induced a small but statistically-significant ( $p < 0.05$ ) increase in chromosomal aberrations in the absence of metabolic activation (concentration range 0.04 to 1.0 mM). Although only the response at the highest dose was significantly higher than the control, there was a positive trend. In the presence of metabolic activation, a larger, dose-related increase ( $p < 0.001$ ) was induced (concentration range 1.0 to 10.0 mM). This effect was confirmed in two repeat experiments. In cells sampled 10 h following treatment, there was no increase in chromosomal aberrations, either with or without metabolic activation.
Test substance	:	Propargyl alcohol, CASNO 107-19-7 purity 97% (source: Aldrich Chemicals)
Reliability	:	(2) valid with restrictions Acceptable Publication
30.12.2002		(1)

### 5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Micronucleus assay
Species	:	mouse
Sex	:	male/female
Strain	:	NMRI
Route of admin.	:	gavage
Exposure period	:	24, 48 and 72 hours
Doses	:	0, 70 mg/kg
Result	:	negative
Method	:	OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year	:	
GLP	:	yes
Test substance	:	
Method	:	Thirty-five seven-week old mice of each sex were randomized into 7 groups containing 5 males and 5 females. Three groups were dosed with test substance at 70 mg/kg, three groups were treated with vehicle and served as controls and one group was treated with the positive control substance Cyclophosphamid at 50 mg/kg. The dosage of 70 mg/kg was determined in a preliminary experiment to be the highest non-lethal dose by this route for these animals.  The test compound dilutions were prepared fresh each day. 175 mg Propargylalkohol was weighed into a 25 ml flask, mixed with deionized water and filled to the calibration mark to make the dosing solutions at 0.7% w/v. Animals were dosed with a volume of 10 ml/kg-bw. Animals were killed by carbon dioxide asphyxiation 24, 48 or 72 hours after application. For each animal, about 3 ml fetal bovine serum was poured into a centrifuge tube. Both femora were removed and the bones freed of muscle tissue. The proximal ends of the femora were opened and the bone marrow flushed into the centrifuge tube. A suspension was formed and centrifuged for 5 minutes at 1200 rpm and almost all of the supernatant was discarded. One drop of the thoroughly mixed sediment was smeared on a cleaned slide, identified by project code and animal number and air-dried for about 24 hours prior to staining.

## 5. Toxicity

Id 107-19-7

Date 31.12.2002

1000 polychromatic erythrocytes were counted for each animal. The number of cells with micronuclei was recorded, not the number of individual micronuclei. As a control measure 1000 mature erythrocytes were also counted and examined for micronuclei. In addition, the ratio of polychromatic to normochromatic erythrocytes was determined. All bone marrow smears for evaluation are coded to ensure that the group to which they belonged remains unknown to the investigator. The number of polychromatic erythrocytes with micronuclei occurring in the 1000 polychromatic erythrocytes counted, and the number of normocytes with micronuclei occurring in the 1000 normocytes counted, were evaluated statistically; comparison of dose groups with the simultaneous control group was performed according to Wilcoxon (paired, one-sided, increase). The results of the treatment groups (test substance) in the micronucleus test at each dose and killing time were compared with corresponding control values. The ratio of polychromatic to normochromatic erythrocytes was also evaluated statistically by the method of Wilcoxon (paired, two sided). The statistical evaluations were performed using the "Diamant" computer program Version 2.0, supplied by the Department of Information and Communication Hoechst AG. All statistical results are based on a 95 % level of significance. Data were also compared with historical controls.

### Remark

Also in support of this finding are data from the National Toxicology Program 90 day mouse study. Micronucleus data were collected from groups of 10 male and female mice exposed to either 0 or 64 ppm Propargyl alcohol for polychromatic erythrocytes; or exposed to 0, 4, 8, 16, 32 or 64 ppm Propargyl alcohol for normochromatic erythrocytes, by inhalation for 90 days. There was no increase in the number or percent of micronucleated cells. (National Toxicology Program, unpublished results)

### Result

All animals survived the administration 70 mg Propargyl alcohol per kg bodyweight. Narrowed palpebral fissures and reduced spontaneous activity were reported the first 2 hours after application, after that, all animals were free of clinical signs of toxicity. The bone marrow smears were examined for the occurrence of micronuclei in red blood cells.

Only the female mice of the 24 and 72 hours killing times showed a very small but statistically significant increase in the number of micronucleated polychromatic erythrocytes. The increase was within the normal range of the negative control values and therefore considered as of no toxicological significance. The number of normochromatic erythrocytes containing micronuclei was not increased. The ratio of polychromatic erythrocytes to normocytes remained essentially unaffected by treatment. Cyclophosphamid induced a marked and statistically significant increase of the number of polychromatic erythrocytes with micronuclei in both males and females indicating the sensitivity of the test system.

Micronulei: Mean polychromatic erythrocytes containing micronuclei were:

Negative control (range)	0.06-0.18%	
Males 70 mg/kg (24 hrs)		0.24%
Females 70 mg/kg (24 hrs)	0.32%*#	
Males 70 mg/kg (48 hrs)		0.04%
Females 70 mg/kg (48 hrs)	0.16%	
Males 70 mg/kg (72 hrs)		0.22%
Females 70 mg/kg (72 hrs)	0.18%*#	
Male Pos control (24 hours)	2.58%*	
Female Pos control (24 hours)	2.24%*	

## 5. Toxicity

Id 107-19-7

Date 31.12.2002

		* = Statistically different from concurrent control. # = within the normal range of historical controls
Test substance	:	Propargyl alcohol, CASNO 107-19-7, purity 99.4% (Containing 0.48% formaldehyde and 0.03% water)
Conclusion	:	Under the conditions of this study, administration of Propargyl alcohol did not lead to a substantial increase in micronucleated polychromatic erythrocytes. It is concluded that Propargyl alcohol is not mutagenic in the mouse micronucleus test.
Reliability	:	(1) valid without restriction Guideline study under GLPs with good documentation.
Flag	:	Critical study for SIDS endpoint
30.12.2002		(19)
Type	:	Micronucleus assay
Species	:	mouse
Sex	:	male/female
Strain	:	C57BL
Route of admin.	:	gavage
Exposure period	:	36 hours after second treatment
Doses	:	24, 48 or 72 mg/kg-bw
Result	:	negative
Method	:	
Year	:	
GLP	:	no data
Test substance	:	
Method	:	Animals: Five 17 week old C57BL mice (Charles River) of each sex were included in each treatment group. Prior to treatment, the animals were acclimatized to the laboratory for several weeks. The handling and treatment of animals were approved by the Health Protection Branch Animal Care Committee, Department of National Health and Welfare.  Treatment: The animals were treated by gavage. Test chemical was dissolved or suspended in USP grade olive oil at a concentration that would allow the delivery of the chemical at a rate of 10 ml/kg bw. Vehicle controls received only olive oil and positive control animals received 45 mg/kg cyclophosphamide by i.p. injection using sterile saline as the vehicle. The doses selected for testing were equal to 25, 50 and 75% of the LD50 determined in a preliminary experiment using the same treatment regimen used in the micronucleus assay. These dose levels were 24, 48 or 72 mg/kg. Mice were treated with test substance twice, 24 h apart, then sacrificed by cervical dislocation approximately 36 h following the second treatment. Bone marrow was collected by flushing one femur from each animal with approximately 0.3 ml fetal bovine serum containing EDTA. The resulting cell suspension was thoroughly mixed using a wooden applicator stick and smears were prepared on clean glass slides. The slides were air dried, fixed in absolute methanol for 5 min, then stained with an Ames Hema-Tek slide stainer using Harleco Wright's stain. 500 polychromatic erythrocytes (PEs) from each animal were scored for the presence of micronuclei. In addition, the ratio of polychromatic to nonochromatic erythrocytes was determined by counting the number of normochromatic erythrocytes (NEs) encountered during the scoring of 500 PEs. The slides were coded and scored blind.

## 5. Toxicity

Id 107-19-7

Date 31.12.2002

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		Micronucleus data were analysed using Chromosomal Aberration Assay Data Management and Analysis System (Version 1.4) and the Micronucleus Assay Data Management and Analysis System (Version 1.4) developed under contract to the U.S. Environmental Protection Agency (Pellom et al., 1990). The criteria for a positive response were: a statistically significant, dose-related increase; and at least one dose that is statistically different from the solvent control.
<b>Result</b>	:	The results showed that Propargyl alcohol did not induce micronuclei in vivo. There was no significant increase in cells with micronuclei. All five males treated with 72 mg/kg twice, died before the scheduled collection of bone marrow. The positive control substance, cyclophosphamide, produced a significant increase in cells with micronuclei.
<b>Test substance</b>	:	Propargyl alcohol, CASNO 107-19-7 purity 97% (source: Aldrich Chemicals)
<b>Reliability</b>	:	(2) valid with restrictions Acceptable Publication
30.12.2002		(12)

### 5.7 CARCINOGENICITY

#### 5.8.1 TOXICITY TO FERTILITY

#### 5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

## 9. References

Id 107-19-7  
Date 31.12.2002

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